NIH: INVESTING IN A HEALTHIER FUTURE

WEDNESDAY, OCTOBER 7, 2015

U.S. SENATE,
SUBCOMMITTEE ON LABOR, HEALTH AND HUMAN SERVICES, AND EDUCATION, AND RELATED AGENCIES,
COMMITTEE ON APPROPRIATIONS,
Washington, DC.

The subcommittee met at 10:04 a.m., in room SD–124, Dirksen Senate Office Building, Hon. Roy Blunt (chairman) presiding.

Present: Senators Blunt, Moran, Shelby, Cochran, Alexander, Cassidy, Capito, Murray, Durbin, Mikulski, Shaheen, Merkley, and Schatz.

OPENING STATEMENT OF SENATOR ROY BLUNT

Senator BLUNT. The Appropriations Subcommittee on Labor, Health and Human Services, Education, and Related Agencies will come to order.

I am certainly pleased we could have this opportunity this morning, Dr. Collins, to talk to you and the other Institute directors about the work you are doing and the work you would like to do.

Every family faces health concerns during their lifetime, and there are so many things that can be done by NIH that I think can't be done as well anywhere else. A new drug, a new device, a new treatment, can take anywhere from a decade to longer to develop. It can cost billions of dollars on occasion, with a pretty high failure rate even when you think you are on the right path.

Certainly, it is necessary for the Federal Government to invest in biomedical research. It represents the hopes of lots of people and lots of families, and particularly now as we see conditions growing as people survive heart problems and stroke problems. We see more people with Alzheimer's and cancer challenges. We see the potential for designer medicine largely because of the great work that was done to figure out how to define and understand the human genome system in a better way.

This year, this subcommittee and the full Committee have placed a high priority on this research. We have planned for and have a bill that includes $2 billion of extra money for that research, an increase of about 7 percent over the current year's spending.

Over the past decade, with not much new money going into NIH, the purchasing power at NIH has decreased by about 22 percent. We hope to see that reversed, if we are successful with what we are trying to do to provide the increase that we are looking at here.

These are clearly difficult budgetary times, and I am sure we could spend a lot of this hearing talking about how there should

be more money for other things in this budget, and there is a disagreement on that in some cases and an agreement in some cases, that if we had all the money in the world, the priorities might be a whole lot easier to achieve.

But I will look forward to hearing from you, Dr. Collins, and from the team that you have brought. As we talked about this morning, I specifically said, can you bring some of the Institute Directors that we haven't seen lately who are very much focused on the individual areas of research, so we can get a greater sense of understanding what the potential is, what the needs are, what is out there that you are seeing and beginning to see?

Also I'd like to discuss the challenge with young researchers having a research grant approved. They are dramatically less than they were a decade ago, and I am sure that that is a topic that we will want to discuss as well. How long do young researchers stay in research, if they continue to have their ideas—not allowed to move forward?

So those are all the things we want to talk about today. We are glad you are here. I want to turn to Senator Murray, who is a big supporter of your work as well for her opening statement.

[The statement follows:]

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STATEMENT OF SENATOR PATTY MURRAY

Senator MURRAY. Thank you very much, Mr. Chairman, especially for your focus on this. I think we all really appreciate it.

Dr. Collins, thank you for being here. I am grateful, as we all are, for all you have done to champion the critical work that NIH does. You have been a great partner, and it is great to see you here.

And thank you to all of your team that is with us today. We look forward to hearing from all of you.

All of us here today agree there is a lot more we need to do to keep our families and our communities healthy, and continue investing in priorities that strengthen our economy from the middle out. The work of the National Institutes of Health is vitally important to that effort. The NIH supports basic research that makes medical advances possible, gives hopes to those living with chronic and life-threatening diseases, and helps drive economic growth and competitiveness.

In my own home State of Washington, we have researchers who are working on ways to repair heart tissue that has been damaged by disease and injury. We have people working on decoding difficult-to-treat forms of breast cancer. We use precision medicine to tackle eye disease and Alzheimer's. The list goes on.

Those are just a few examples of the incredible work done to improve health and well-being for families across the country and really around the globe.

At the same time, the life sciences are helping to drive economic growth and job creation. In my State, the life sciences sector directly employs 34,000 people, making it the fifth largest employment sector in my State.

The investments that we make in NIH and education and other programs under this subcommittee's jurisdiction that support the life sciences indirectly will help our economy create the jobs of the 21st century and help ensure a workforce that can take them on.

That is why, like Chairman Blunt, I see maintaining our country's central role in the life sciences as a top priority, and Federal investments in medical research could not be more important to this effort. Supporting medical research starts with making sure shortsighted budgeting does not get in the way. For far too long, we have seen inflation erode Federal investments in R&D, making it harder for researchers to get the support they need.

In fact, I know that you, Dr. Collins, have said that, increasingly, the NIH is having to turn promising projects away. For patients and families who are waiting and hoping for medical breakthroughs, that is unacceptable.

I am very proud that in late 2013, Democrats and Republicans were able to reach a budget agreement to roll back sequestration for fiscal years 2014 and 2015. As we all know, that deal expired last week, which means Congress is going to once again have to come together and find a solution.

As I have made clear, I believe that we need an agreement that builds on the bipartisan foundation set in the budget deal from last Congress, rolls back the cuts to defense and nondefense investments equally, and protects priorities that are essential to promoting a strong and growing middle class, like research and education and infrastructure.

I have been encouraging my colleagues on the other side of the aisle to come to the table to work with us so that we can reach another bipartisan budget deal and avoid those automatic cuts that impact these and other important investments in our country's future. I am also currently working with Chairman Alexander, who is here today, on the HELP Committee on a bipartisan initiative to advance medical innovation. That is an effort that is very much related to the conversation today. I see that initiative as an opportunity to help patients get the best, most effective cures and treatments as quickly as possible while upholding the highest standards of consumer and patient safety.

And to me, a central part of accomplishing this goal and tackling the tough medical challenges our country faces is making sure that research and development can thrive.

I am pleased that so far we have seen bipartisan interest in ramping up investments in the NIH and FDA, and I have made clear that I will only support a bill that does just that. I am going to be very focused on finding a path forward on this goal in the coming weeks because, put simply, stronger investment in medical research mean a stronger, healthier country.

So I am hopeful that Republicans and Democrats can come together to build on the bipartisan foundation we set in the budget deal last Congress and make the investments we need to seize these and other opportunities in a way that helps our economy and our country work better for our families.

Thank you, Mr. Chairman.

Senator BLUNT. Thank you.

Before I yield to Dr. Collins for his opening statement, I have received a statement from full committee vice chairman, Senator Mikulski. Her statement will be inserted into the record at this point.

[The statement follows:]

PREPARED STATEMENT OF SENATOR BARBARA A. MIKULSKI

Thank you, Chairman Blunt and Ranking Member Murray for holding this important hearing today. I also want to thank our witnesses, Dr. Francis Collins, our brilliant and tireless NIH Director, as well as all the NIH Institute Directors before us today, including Dr. Douglas Lowy, Acting Director of the National Cancer Institute who will likely one day receive a Nobel Prize for his work on the HPV vaccine.

I am so pleased we're here today to talk about an issue very close to my heart: the National Institutes of Health. I call it the National Institutes of Hope. When we invest in NIH, we see better cures and treatments for diseases and conditions that devastate families and drive up health costs, from Alzheimer's and autism to diabetes, heart disease, and cancer.

The NIH is a world-class institution responsible for turning scientific discoveries into better health for us all. Because of the work at NIH, we have cut the cancer death rate by 11 percent in women and 19 percent in men. Deaths from heart attack and stroke have been reduced by 70 percent in the past 60 years. A child born today will likely live to be 78 years old—nearly three decades longer than a baby born in 1900.

That's just the start of NIH breakthroughs. In 2013 alone, NIH was a major source of support for eight of the 10 most highly touted scientific discoveries of the year. Not a bad year's work! But I know and I hope that more is to come.

As Chair of the Appropriations Committee, I've been pleased to secure funding increases for NIH in recent years, including a $1 billion increase in fiscal year 2014 and a $200 million increase in fiscal year 2015. But it's not enough. Over the past 10 years, NIH funding has not kept pace with inflation leading to a 20 percent reduction in purchasing power for NIH. Adjusted for inflation, NIH actually receives nearly 25 percent less funding today than it did in 2003.

This is quite simply unacceptable. At a time when so many other countries are ramping up their investments in biomedical research, the U.S. is scaling back. We must find a way to provide NIH with stable and reliable funding increases in order to advance life-saving medical research for patients worldwide.

Lifting budget caps is the most appropriate solution. By doing so, we lift all boats. We cannot just life caps for defense spending. That doesn't help NIH. We must also lift caps for non-defense spending—for NIH, FDA and CDC. Because defense of this country doesn't just mean troops on the ground or drones in the air. Defense of this country also means helping defend families in their fights against the very real diseases that touch their lives every day, like cancer, Parkinson's, ALS and Alzheimer's. The only way to help those families is to lift the caps. These current budget caps are caps on innovation, caps on progress, caps on cures, caps on new treatments and caps on how far NIH can go.

That's why I've been fighting for a 2-year budget deal that lifts the caps equally for non-defense spending. Now that we have a CR in place through December 11, it is time for Leaders across the aisle and across the dome to come together. It's time to get a budget deal worked out. One that ends sequester and lifts the caps. A budget deal would pave the way for this Appropriations Committee to put together a government spending bill that makes sense.

Without a budget deal, we are stuck. There is simple no way for this Committee to respond to the needs of American families under the current caps. Case in point is the fiscal year 2016 Labor-HHS bill reported out of this committee.

Chairman Blunt did his best considering the limited funding he was given. But he had to rob Peter to pay Paul. Yes, he was able to give NIH a $2 billion increase. But in order to do so he had to cut funding form the Social Security Administration, which would have to close down field offices and processing centers, making it harder for people to get their Social Security checks. He had to gut the Corporation for National and Community Service, which helps improve education from pre-school up, recover and rebuild communities from natural disasters, and supports veterans and military families during deployment. He also had to cut the Centers for Medicare and Medicaid Services, making it harder for seniors, children and those of modest means access needed healthcare services.

But I also know that NIH cannot be expected to accomplish our shared goals if they are operating paycheck to paycheck, crisis to crisis, shutdown to shutdown. They need stable and reliable funding. They need to know that their budget can support multi-year grants. They need to be able to tell young researchers that the United States Government values them and will support their work in years to come.

A budget deal is the only way to get this done.

Thank you.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

Senator BLUNT. Dr. Collins, if you want to make an opening statement and a brief review of the team you brought with you, we won't count that against your opening time.

STATEMENT OF FRANCIS COLLINS, M.D., Ph.D., DIRECTOR

ACCOMPANIED BY:

DOUGLAS LOWY, M.D., ACTING DIRECTOR, NATIONAL CANCER INSTITUTE

GRIFFIN P. RODGERS, M.D., M.A.C.P., DIRECTOR, NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES

WALTER J. KOROSHETZ, M.D., DIRECTOR, NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE

JON R. LORSCH, Ph.D., DIRECTOR, NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES

NORA D. VOLKOW, M.D., DIRECTOR, NATIONAL INSTITUTE ON DRUG ABUSE

Dr. COLLINS. Thank you, Mr. Chairman. Yes, I would be glad to introduce the folks at the table with me. We are happy at NIH that we have a deep bench of really remarkable scientist leaders. Of the 27 institutes and centers, you will see in front of you here five of those leaders.

INTRODUCTION OF NIH INSTITUTE DIRECTORS

Starting to my left, your right, Dr. Jon R. Lorsch, the Director of the National Institute of General Medical Sciences (NIGMS), an Institute which is, by the way, having a pretty big day today because the Nobel Prizes in chemistry were given to, 2 out of 3 scientists NIGMS supported for 30 or 35 years, a nice moment for NIGMS.

Next to Dr. Lorsch, Dr. Walter Koroshetz, who is the Director of the National Institute of Neurological Disorders and Stroke, a distinguished neurologist and basic scientist as well as a clinician.

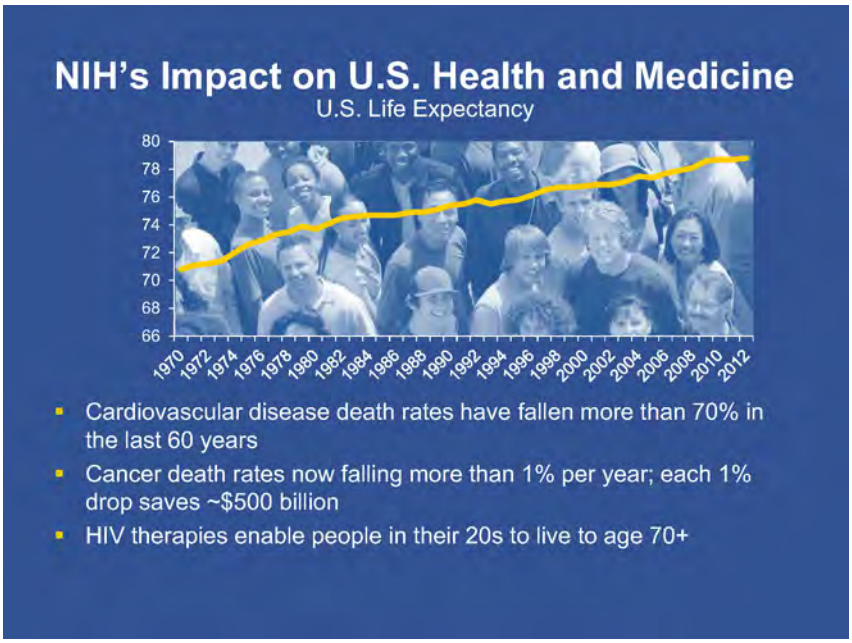
Over here on my right, Dr. Douglas Lowy, who is the acting Director of the National Cancer Institute, much recognized for his work in the development of a vaccine against HPV, which is saving many lives from cervical cancer and other cancers.

Next to Dr. Lowy, Dr. Griffin P. Rodgers, Director of the National Institute of Diabetes and Digestive and Kidney Diseases, and also one of those folks who is being honored this evening at the Sammies Awards because he is one of the nominees for this year's awards for public service.

And over on the far end, Dr. Nora D. Volkow, a highly regarded scientist in the area of addiction science and the science of the brain, who serves as our able and highly recognized (by the press), because she often is in front of them talking about addiction, Director of the National Institute on Drug Abuse.

That is my team. Now, I will maybe let you start the clock, and I would like to tell you a few things by way of an opening statement.

It is a great honor, for my colleagues and me, to be here before you to discuss how NIH is investing in a healthier future for all Americans.



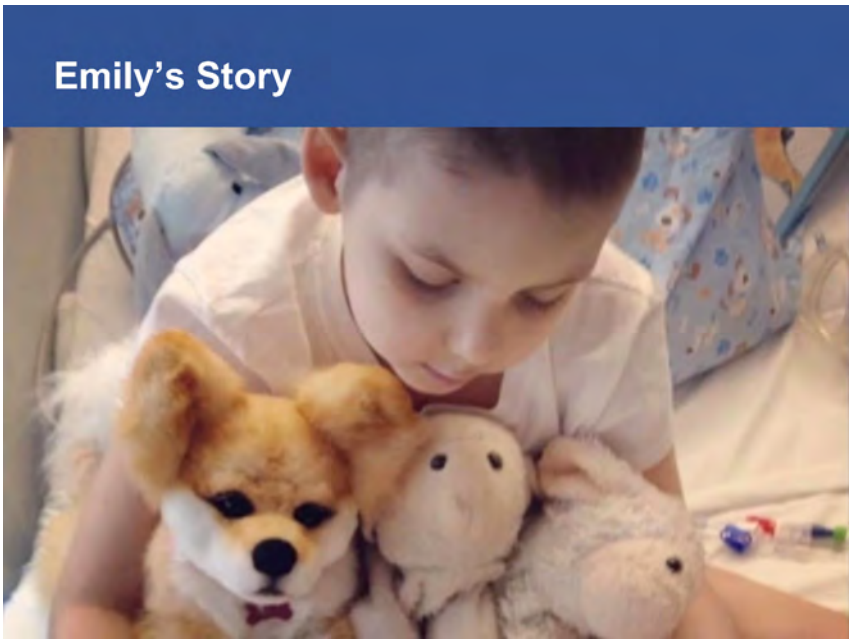
Longevity, you can see here what has happened. Breakthroughs generated by NIH-supported research are behind many of the gains our country has enjoyed in health and longevity. For example, cardiovascular diseases, death rates have fallen by more than 70 percent in the last 60 years. Cancer death rates are now dropping by 1 percent to 2 percent annually. Likewise, HIV/AIDS originally when first being written about as a death sentence, now treatments greatly extend lives, and prevention strategies and the increasing potential of an effective vaccine are enabling us to envision in real terms, the first AIDS-free generation.

So, on behalf of NIH, our employees, our grantees, the patient community, I want to thank all of you for your continued support and for holding this hearing today. We see in front of us, a remarkable landscape of biomedical opportunities powered by exceptional advances in scientific knowledge and technological innovation.

This morning's announcement of those Nobel Prizes in chemistry for studies of DNA repair is a compelling example of how these investments have been paying off, building upon work that has gone on over decades.

EMILY WHITEHEAD'S STORY AND HISTORY OF CANCER IMMUNOTHERAPY

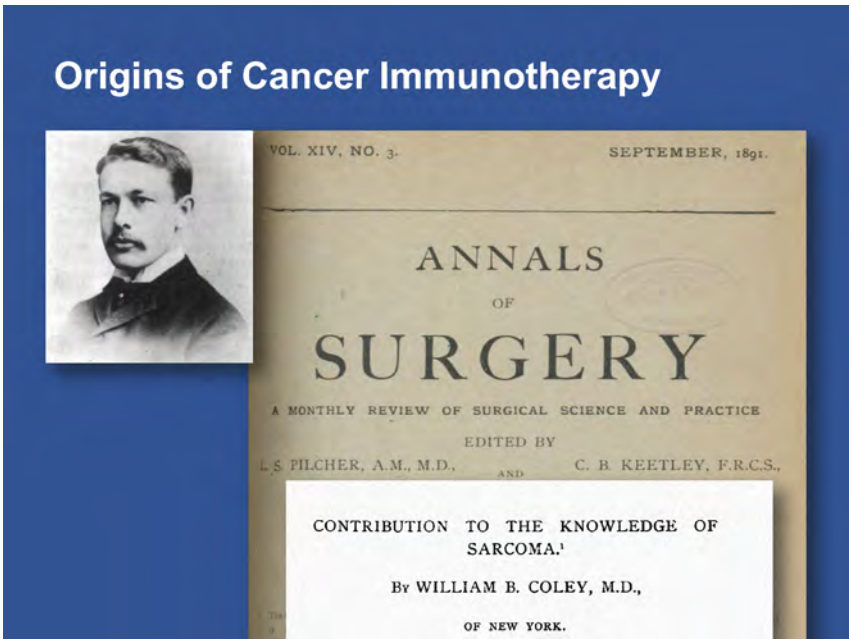
I would like to share with you this morning an inspiring story, another one that has emerged from decades worth of NIH-funded basic research. This is the story of cancer immunotherapy, a treatment that involves harnessing the body's own immune system to fight this dreaded disease.



So, I would like you to meet Emily. Emily Whitehead, back in 2010 when this photo was taken, she was struggling with acute lymphoblastic leukemia, a disease that, thanks to advances made possible by NIH, chemotherapy can cure 90 percent of the time.

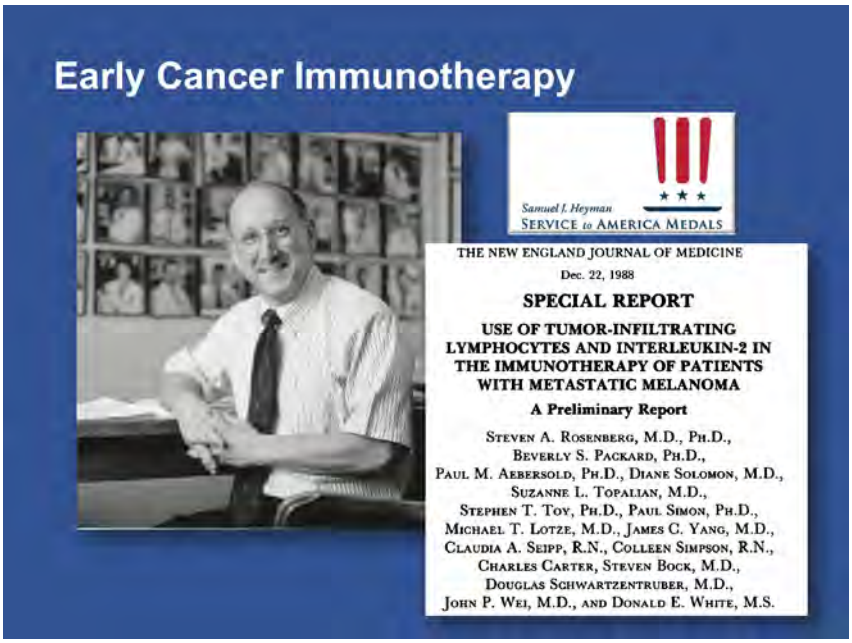
Unfortunately, Emily was in the other 10 percent. Her prognosis after failed chemotherapy was grim. But, doctors at Children's Hospital of Philadelphia approached her parents about trying something radically different, a clinical trial of an experimental approach called immunotherapy.

So, I would really like to use this story to make a point about the long arc of medical research involving many investigators and many years of work, ultimately leading to Emily.



Let's take a brief journey back in time. The history of cancer immunotherapy can be dated actually back to the 1890s. A New York surgeon, Dr. William Coley, reported success in treating a few inoperable cancers by stimulating patients' immune systems with bacterial toxins.

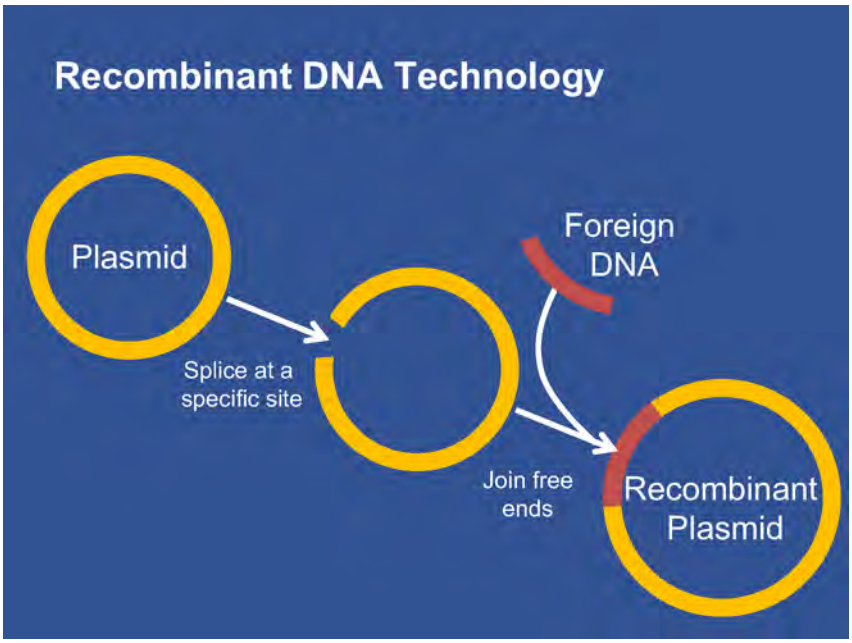
But, his results were highly variable. The treatment was very toxic. And this approach largely fell by the wayside until the mid-1980s.



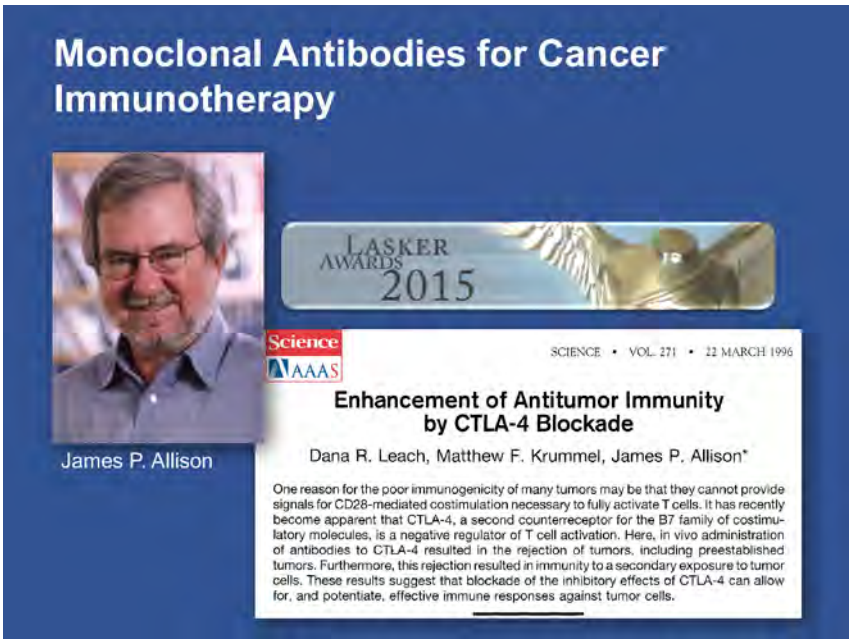
Then, at the National Cancer Institute, Dr. Steven Rosenberg explored the ability of certain immune cells called cytotoxic T cells to destroy tumor cells. He wondered why the immune system does not recognize cancer cells all the time and eliminate them, and whether the immune system could be helped to do this by taking these T cells out of the body, stimulating them with an activating factor, and then re-infusing them to the cancer patient.

It did not always work, but there were some dramatic responses.

Dr. Steven Rosenberg was and is a true pioneer. In a wonderful stroke of timing, Steven was named this morning as the Federal employee of the year by the Partnership for Public Service and will be recognized in the Sammies Award ceremony this evening.



Meanwhile, the recombinant DNA revolution was gathering momentum. Basic research spearheaded, again in large part by NIH, led to the discovery of methods to splice fragments of DNA together, giving birth to the whole field of biotechnology.



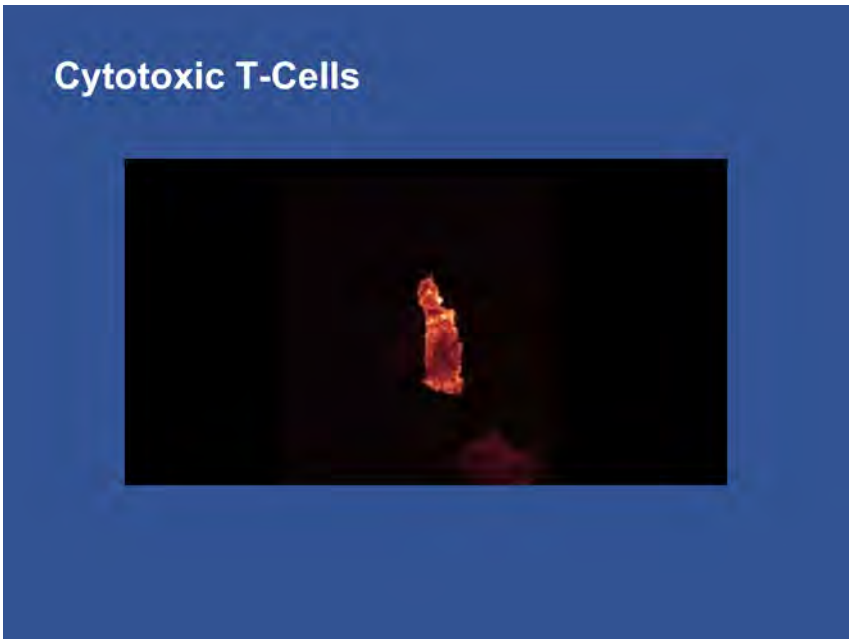
Armed with this powerful set of tools and technologies, NIH-supported researcher Dr. James Allison pioneered one particular form of cancer immunotherapy. He discovered that a particular protein on the surface of those T cells actually acts as a braking system, preventing the full activation of the immune system when a cancer is emerging.

By designing and delivering an antibody that blocks that protein, Dr. Allison showed the brakes could be released. Dramatic responses to previously untreatable cancers began to appear.

Again, another award. Dr. Allison just received the Lasker Award, America's Nobel Prize, for this work last month.

Building on this growing momentum, other scientists like Dr. Carl June at the University of Pennsylvania, who is one of Emily's doctors—and his lab, I know, Chairman Blunt has recently visited—have been busy designing even more precise cancer immunotherapies.

In the approach designed by June's group, T cells are collected from cancer patients and engineered in the lab using recombinant DNA so that they can produce special proteins on their surface, called chimeric antigen receptors, or CARs. When those modified cells are infused back into patients, they multiply. With guidance from their newly engineered receptors, they seek and destroy the tumor cells.



Let me just show you how these killer T cells seek and destroy cancer cells with a quick video. This is pretty dynamic, and the results can be dramatic.

So, that is a T cell that you see, there lit up in red. It is busy migrating around on this Petri dish. It is looking for foreign invaders.

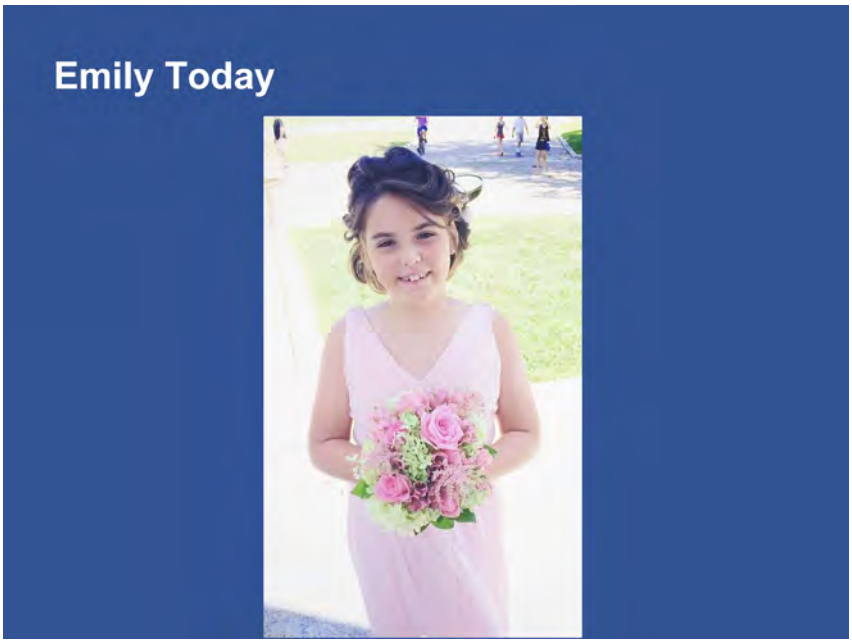
Now you will see when it finds a cancer cell, it is going to get really excited. There, you see the cancer cell in blue, the T cell really going after it.

Now I'm going to change the colors on you in this next little clip. The T cells are now in green, and the cancer cells are red. Watch for the red flash. That is where the T cell just ruptured the membrane of the cancer cell and sent it off to the cancer cell graveyard. You can watch this happening repeatedly with different cancer cells being targeted by these T cells that go after them and figure out how to do away with them.

You can see why one of Dr. Steven Rosenberg's recent patients refers to those T cells as little ninja warriors. They do their job.

This is not just the future of cancer treatment; it is the present. But again, note that this was built on decades of work. In fact, going back to Dr. Allison, a recent analysis shows that the pathway that led to his Lasker Award included the contributions of 7,000 scientists over more than a century, with many of those scientists pursuing basic questions that had no apparent connection to cancer.

So, I tell you this story to emphasize the critical need for Federal investment in this whole spectrum, from basic to translational to clinical research. If we do that, we can realize our vision of accelerating discovery across this vast landscape of biomedicine, and ultimately save many lives.



Remember little Emily? Here she is today, a junior bridesmaid, the picture of health. This happy picture made possible by her parents' decision to go ahead and enroll her in that pioneering cancer immunotherapy trial. Twenty-eight days after that treatment, Emily was cancer-free. And more than 5 years later, she remains cancer-free.

Emily is just one success story. I can tell you many more, including all these folks across the entire NIH portfolio, about how basic scientific inquiry is leading to a healthier future for all Americans, from the development of neurotechnologies through the Brain Initiative, to the million or more cohort person in the Precision Medicine Initiative that will generate knowledge applicable to an entire range of health and disease.

I would say, our future has never been brighter. But to realize that future, NIH needs your sustained support.

So thank you, Mr. Chairman. My colleagues and I very much welcome your questions.

[The statement follows:]

PREPARED STATEMENT OF FRANCIS S. COLLINS, M.D., PH.D.

Good morning, Chairman Blunt, Ranking Member Murray, and distinguished members of the subcommittee. I am Francis S. Collins, M.D., Ph.D., and I am the Director of the National Institutes of Health (NIH). It is an honor to appear before you today to discuss how NIH is investing in a healthier future for all Americans.

NIH has been advancing our understanding of health and disease for more than a century. Scientific and technological breakthroughs generated by NIH-supported research are behind many of the improvements our country has enjoyed in public health. For example, our Nation has gained about 1 year of longevity every 6 years since 1990.[1] A child born today can look forward to an average lifespan of about 78 years—nearly three decades longer than a baby born in 1900. Deaths from heart attack and stroke have been reduced by more than 70 percent in the past 60 years. Thanks to NIH-developed anti-viral therapies, HIV-infected people in their 20s today can expect to live into their 70s. This compares to a life expectancy measured in months when the disease first appeared in the 1980s. Cancer death rates have been dropping about 1 percent annually for the past 15 years. These are extraordinary strides—but we aim to go much further.

On behalf of NIH, our employees, grantees, and patient community, I want to thank the Members of this Subcommittee for your continued support, and for holding this hearing today.

This investment could not come at a better time. We are in the midst of a remarkable stream of scientific advances spurred by dramatic advances in biotechnology. Today, I want to share with you a few of the many promising opportunities before us that will lead to a healthier future for all. I can assure you that the future of scientific research has never been brighter.

[1] Http://www.cdc.gov/nchs/data/nvsr/nvsr64/nvsr64 02.pdf.

Many recent breakthroughs stem from our Nation's commitment to investing in basic science research. Basic science lays the foundation for advances in disease diagnosis, treatment, and prevention by providing the building blocks for clinical applications. Basic science is generally not supported in the private sector, and NIH's focus on understanding fundamental biological processes fosters innovation and ultimately leads to effective ways to treat complex medical conditions. But the lead time for medical breakthroughs to arise from basic science research is often measured in decades, and it is generally not possible to predict which basic investigations are going to be the most fruitful in the long run. NIH's successful investment in basic science is reflected by the awarding of 145 Nobel prizes to NIH-supported scientists; the vast majority of these individuals were recognized for basic science advances.

A compelling example of how we are trying to unravel life's mysteries through basic science is with the Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative. With nearly 100 billion neurons and 100 trillion connections, the human brain remains one of the most daunting frontiers of science and one of the greatest challenges in medicine. This bold, multi-agency effort to revolutionize our understanding of the human brain will require the development of entirely new technologies. Engineers, computer scientists, nanotechnologists, physicians, and neuroscientists will need to work together and challenge the limits of their respective fields of science. By measuring real-time activity at the scale of complex neural networks in living organisms, we can explore how the brain enables the human body to record, process, utilize, store, and retrieve vast quantities of information—all at the speed of thought. Ultimately, the foundation of understanding developed by the BRAIN Initiative will help reveal the underlying pathology in a vast array of brain disorders and provide new therapeutic avenues to treat, cure, and prevent neurological and psychiatric conditions such as Alzheimer's disease, autism, schizophrenia, depression, epilepsy, and addiction.

Five years ago, a project like this would have been considered impossible. But with your support, it is now underway. The first two rounds of grant awards have been made—and they are tremendously exciting. In the year since the inaugural round of awards, totaling $46 million, was issued, several exciting new tools and techniques have been developed for studying brain structure and function. One such technique, called Drop-Seq, groups neurons based on the genes that they express, getting us closer to having a complete parts list for the brain. Another tool, called DREADD (Designer Receptors Exclusively Activated by Designer Drugs), used designer drugs to turn on and off genetically engineered neural receptors. While its inventors used DREADD to precisely control a mouse's motor movements, the tool may potentially provide a way to restore proper neural function. Among the second round of awards, totaling $85 million, announced last week are projects aimed at delivering targeted electrical pulses to the brain to treat illnesses such as traumatic brain injury and epilepsy, as well as collaborations with physicists towards building non-invasive tools that can observe neural activity deep within the brain with unprecedented spatial detail.

We need to continue to ramp up this effort, and we need your support for that, as requested in the President's Budget. While the goals of this initiative are ambitious, the time is right to inspire a new generation of neuroscientists to undertake this groundbreaking approach to understanding the human brain.

Another area of exceptional scientific opportunity I want to highlight today involves one of our Nation's most feared killers: cancer. Until recently, our weapons for attacking cancer have been largely limited to surgery, radiation, and chemotherapy—all of which can be effective, but carry risks and toxicities. Now, after years of intense basic and translational research, we have two exciting new possibilities: targeted therapeutics and cancer immunotherapy. I want to particularly focus on the latter.

Researchers have long been puzzled by the uncanny ability of cancer cells to evade the immune response. What stops the body from waging its own "war on cancer?" As it turns out, our bodies have important built-in checkpoints to prevent our immune systems from running amok and killing healthy cells. Certain white blood cells called T-cells—the armed soldiers of the immune system—are designed to go after foreign invaders, but they also need a stop signal to prevent going into overdrive. One way to do this is through a receptor on the T-cell called CTLA–4 that inhibits its function. Tumor cells have figured out how to take advantage of this pathway by upregulating CTLA–4; the result is to put the brakes on the immune system, giving the green light for the cancer to grow.

NIH-funded researchers have discovered a way to release the brakes by introducing a monoclonal antibody against CTLA–4, allowing the normal immune response to be re-activated. Dr. James Allison, who led the basic science efforts that led to these insights, was just honored with the receipt of the Lasker Award, the

"American Nobel Prize." Promising results in patients with metastatic melanoma and lung cancer are making this and other immunotherapies the breakthrough treatment of the future. After President Carter was diagnosed with stage 4 metastatic melanoma, he received immunotherapy as part of his treatment.

A final area I wish to highlight is precision medicine. As you know, in his State of the Union address in January of this year, President Obama announced his intention to launch the Precision Medicine Initiative (PMI). This is a bold new research effort to revolutionize the prevention and treatment of disease, and I thank the Committee for including the requested $200 million for PMI in its fiscal year 2016 appropriations bill. We believe that the time is right for this audacious undertaking, and, with your support, the NIH and our HHS partners, the U.S. Food and Drug Administration (FDA), the Office of Civil Rights, and the Office of the National Coordinator for Health Information Technology (ONC), will work with great intensity to achieve this vision.

Historically, physicians have had to make most recommendations about disease prevention and treatment based on the expected response of the average patient. This one-size-fits-all approach works for some patients and some conditions, but not others. Precision medicine is an innovative approach that takes into account individual differences in patients' genes, environments, and lifestyles. This concept is not new; blood typing, for example, has been used to guide blood transfusions for a century. Prescription eyeglasses are tailored specifically to the patient's individual needs. Moreover, the identification of the BRCA1 and BRCA2 genes has made it possible to provide options for women at high risk for breast and ovarian cancers. And, the gene implicated in cystic fibrosis has led to widespread availability of screening and targeted therapeutics.

The prospect of applying this concept broadly to virtually all diseases, and to disease prevention, has been dramatically improved by the development of powerful and affordable methods for characterizing personal biological attributes (such as genomics and metabolomics), the widespread adoption of electronic health records, the recent revolution in mobile health technologies, and the emergence of computational tools for analyzing large biomedical data sets. These advances will help make possible the dream of personalizing a wide range of health applications.

With this in mind, we are excited to take a lead in the two key components of the President's Precision Medicine Initiative that will be managed by NIH. First is a near-term goal that will focus on cancer, building on advances in genomics and immunology that make it increasingly possible for specific therapies to be designed for the individual, based on the precise molecular characteristics of their tumor. Second is a longer-term aim to generate knowledge applicable to the whole range of health and disease. Both components are within reach, due in large part to recent scientific breakthroughs. Let me tell you just a little bit more about the longer term project.

In order to achieve the President's ambitious plan, NIH will build a large national research cohort of one million or more Americans that will provide the platform for expanding our knowledge of precision medicine approaches and benefit the Nation for years to come. These volunteer participants will agree to share health information, provide biospecimens, and wear sensors that will detect environmental exposures and body performance—all with appropriate privacy protection. They will be true partners in this research. Not subjects, not patients— partners. They will play an active role in how their genetic, environmental, and medical information is used for the prevention of illness and management of a wide array of chronic diseases. The goal will be to expand the benefits of precision medicine into myriad aspects of health and healthcare. Participants will be at the center of the project design, and they will have access to their own health data, as well as research using their data, to help inform their own health decisions. Through this dynamic community, researchers will be able to advance the information derived from this cohort into new knowledge, approaches, and treatments. Researchers from many organizations will, with proper protection of patient information, have access to the cohort's data so that the world's brightest scientific and clinical minds can contribute insights.

In order to help inform the vision for building the national research cohort of one million or more volunteers, I formed a Precision Medicine Initiative Working Group, as part of my Advisory Committee, to develop a specific design plan for creating and managing such a research cohort. To help carry out its charge, the Working Group engaged with stakeholders and members of the public through workshops and requests for information, focusing on issues related to the design and oversight of the cohort. Public engagement, as well as internal discussions, led to the vision for the design and utility of the program, and the Working Group released their report just three weeks ago. The report includes recommendations in six areas critical to the development, implementation, and oversight: cohort assembly, participant engage-

ment, data, biobanking, policy, and governance. We plan to move swiftly to build the infrastructure so that participants can begin enrolling in the cohort in 2016, with a goal of at least one million participants by 2020.

A project of this magnitude will lay the foundation for a myriad of new prevention strategies and novel therapeutics. Although the initiative will likely yield its greatest benefits years down the road, there will be successes in the relatively near future as well. Moving forward, this pioneering research initiative will require the involvement of many different sectors of science and society, including biologists, physicians, technology developers, data scientists, healthcare organizations, and, most importantly, the American people. Given related efforts in a few other countries, we will aim to forge collaborations on a global scale.

With sufficient resources and a strong, sustained commitment of time, energy, and ingenuity from the scientific, medical, and participant communities, precision medicine's full potential can be realized to give everyone the best chance at good health. There's no better time than now to embark on this ambitious new enterprise to revolutionize medicine and generate the scientific evidence necessary to move this individualized approach into everyday clinical practice.

Today, I have outlined for you just a few of the very many promising scientific opportunities on the horizon. With your support, the future of medicine can be very bright. This concludes my testimony, and my colleagues and I look forward to answering your questions.

Senator BLUNT. Well, thank you very much, Dr. Collins. I am certainly glad you are here.

CURE VS. TREATMENT

Let me ask a couple questions. Senator Toomey and I went to see what Dr. Carl June was doing. That effort, you can correct me where I am wrong here, very much focused on what the individual patient needs. Dozens of individual patients at all age groups have seen success in that particular effort.

But two thoughts about that. One is, is this likely in cases like this to go beyond treatment to the level of where, in this particular case, this particular fighting agent is always there, so you are talking about a cure instead of treatment? I would be interested in what discussion is going on, how we look at a world where cure is one of the options as opposed to a healthcare world that has largely been defined by treatment up until now.

I will just go ahead and ask my second question at the same time, which is, on these individual cases, I would assume at some point one of the challenges is what we do that makes that most likely to be scalable, so that every patient does not have all of the expense of a unique treatment, but a scalable effort made that will come naturally.

But talk to me about those two things, and whoever you would like to answer those questions.

Dr. COLLINS. Those are great questions, Mr. Chairman. I think I will turn to Dr. Lowy as the acting Director of the National Cancer Institute, who is investing in big ways in cancer immunotherapy, to address both of those.

Dr. LOWY. Thank you, Senator Blunt.

This is really a critical juncture right now because we have opportunities for long-term responses. And what you are asking is, are a subset of those responses going to lead to cure? And we certainly are optimistic and hopeful that this will happen, at least in some cases.

We need to understand better, as you point out, what the mechanisms are that drive the important clinical responses to immunotherapy. And if we can understand them better, we may be

able to devise even more effective immunotherapies that also will have fewer side effects.

That is an area that we really are actively supporting investigations in, because we do hope eventually that we can get to the area of precision and predictive oncology where patients, we know what treatment to give to them and we know what kind of immunotherapy to give to them, in addition to targeted treatments. Thank you.

Dr. COLLINS. In terms of the scalability, which is a tough question for some of the very personalized immunotherapy that you saw in Carl June's lab, there are certainly strong interests in companies in figuring out how to do this, where you can, in fact, make this available to thousands of patients instead of in small trials. We would think that is a very appropriate kind of place for public-private partnerships to spring up, so that this idea of engineering your own T cells to go after your cancer could be done for more and more individuals.

Senator BLUNT. I would just say, before I turn to Senator Murray, that this is a topic that I am having some discussions with people representing health insurance companies. Are you thinking about a future where traditional treatment may be less expensive initially but a long-term potential cure more expensive initially but less expensive over time? What are your standards going to be? Are you thinking what we can do now?

Really, the whole concept, I am sure we will get to, of designer medicine, what can happen with the efforts, Dr. Volkow, on the brain and how that those impacts?

I think we will have time for more than one round of questions. We have a couple people on a timeframe. We will try to get to them quickly. We will do this by order of both appearance and, if you were here on time, seniority on the committee.

The first person to go to is Senator Murray.

Senator MURRAY. Thank you very much, Mr. Chairman.

EFFECT OF YEAR-LONG CONTINUING RESOLUTION ON NIH RESEARCH

Dr. Collins, as you know, we are working on a continuing resolution until December 11. I wanted to ask you, what effect would a yearlong CR at the current rate have on the NIH research?

Dr. COLLINS. Believe me, we are thinking and worrying a lot about that. We are in a circumstance where, perhaps emboldened by the enthusiasm, we have seen in both the Senate and House in fiscal year 2016 budget process, I have a number of very exciting initiatives that we would like to launch in fiscal year 2016, the Precision Medicine Initiative, which I am sure we will talk about in the course of this hearing; the BRAIN Initiative, which is already underway now for 2 years but is at a critical point to ramp up and build on what has already been done; the ability to be able to push our vaccine strategies for influenza, for HIV/AIDS. All of those are at a critical point where more investment is needed.

We have been heartened, greatly, by the actions of this Committee and a similar Committee in the House to believe that we might have the chance to do these things.

A yearlong CR, unless an anomaly were possible for NIH, would be simply devastating. The Precision Medicine Initiative, for in-

stance, would basically have to go into the freezer or on mothballs or whatever the appropriate discouraging metaphor would be.

We would just be at the point of starting this effort to enroll 1 million Americans in this unprecedented study and carry out exciting new studies in cancer genomics, and those would basically have to go on hold. That would be enormously disappointing.

Similarly, imagine the BRAIN Initiative, which is on this exciting ramp. It would, basically, have to take a pause for a year just at the point when the momentum is building.

I cannot emphasize enough how much we are worried about this. We can struggle along with the CR until December 11, but if it is a yearlong CR without an anomaly, it is going to be a dark day, indeed, a dark year, indeed.

Senator MURRAY. Thank you very much.

SHORTAGES IN TREATMENT CENTERS

Dr. Volkow, more than 20 million people in the United States have a substance abuse problem. We know that only a small percent of that population will get help and that those looking for treatment often cannot find it because of long waiting times for care or because of limited insurance coverage.

The work that National Institute on Drug Abuse (NIDA) does to address addiction is critical, but I really worry that cutting funding for treatment and recovery, as the Subcommittee's 2016 bill would do, would make it very hard for addicts to get the help they need, especially at a time when 44,000 more Americans now die annually from overdoses than they do in car crashes.

The substance abuse block grant that represented 42 percent of State spending on substance abuse as recently as 2007, that share would likely drop to below 32 percent under this subcommittee's bill.

I wanted to ask you, and take advantage of you being here today, are you seeing shortages in treatment services around the country for addicts who want help? If so, does that concern you?

Dr. VOLKOW. Unfortunately, the answer is yes. Of course, it concerns us, because the problem of drug addiction is actually one that has been increasing in our country. We have known all along that only 15 to 20 percent of those addicted receive treatment.

Senator MURRAY. Fifteen percent?

Dr. VOLKOW. Fifteen percent.

Senator MURRAY. Only 15 percent of the people who ask for help?

Dr. VOLKOW. No, 15 percent of individuals that have addiction receive it. Not all of them search for treatment, but one of the reasons they do not search for treatment is they are discouraged by the lack of infrastructure to support their needs, as well as the issue of stigma.

So those are two aspects that have made it very, very difficult to provide treatment.

What NIDA is doing is trying to take advantage of infrastructure that we have in our country to maximize their involvement in substance use disorders. That includes the healthcare system, the criminal justice system. Those two are structures that we are engaging to provide with evidence-based treatment that can improve outcomes.

BRAIN INITIATIVE AND CANCER RESEARCH

Senator MURRAY. Dr. Koroshetz, I wanted to ask you, I know the BRAIN Initiative recently released its second round of awards, bringing NIH investment to $85 million for 2015. Can you tell us about the progress you have already made under the BRAIN Initiative?

Dr. KOROSHETZ. Yes, happy to do so. The BRAIN Initiative is incredibly exciting. It is off to a great start, as Francis mentioned. The center of the BRAIN Initiative is developing new technologies to allow us to monitor, interrogate, and also modulate brain circuit activity. If you think about it, that is really what patients are suffering from, disorders in brain circuitry activity.

The problem is that we do not have the technologies to modulate those circuits except in a very unsophisticated manner. So some things have already come out that are really, really exciting.

A couple of examples, there is a new technology, in which you can put an artificial gene into particular neurons in the brain, and with a drug that has no other effects you can turn on or turn off precisely certain neuron types in the brain. This is really an amazing feat to be able to do that.

Contrast that with treatment for Parkinson's disease, where a wire is put into the brain and an electric current is sent in, and it goes willy-nilly. No one knows exactly what it is doing, but it turned out to be quite effective.

You can just imagine how these new precision technologies can completely change how we can basically normalize or cause compensation in brain circuits for patients' neurologic deficits. So it is really quite exciting.

Senator MURRAY. Thank you.

Unfortunately, my time is up, so I will wait for the second round.

Senator BLUNT. We are fortunate to have the chairman of the full committee and the ranking member of the full committee with us.

Senator Cochran.

COMBATING DIABETES

Senator COCHRAN. Mr. Chairman, thank you.

In my State of Mississippi, we have one of the highest rates of type 2 diabetes in the Nation. We are told that over 12.5 percent of our State's adults have the disease, and the problem is growing rapidly.

Are there any new approaches that you have in mind in dealing with hotspots, outbreaks, whatever you want to call it, in areas like our State?

Dr. COLLINS. That is a great question for Dr. Rodgers, since his institute oversees diabetes research at NIH.

Dr. RODGERS. Thank you, Senator, for the question.

Type 2 diabetes is increasing at an alarming level. There are currently about 29 million people in the U.S. with diabetes and 86 million who have prediabetes. There are two things that we're doing about that.

Number one, for people who have established diabetes, there is a common drug that is started on patients called metformin. But

unfortunately, in the great majority of patients, that drug will no longer be effective.

We've started a trial in which we are characterizing the combination of metformin with one of four different classes of drugs to see what the next effective drug would be for given individuals. This is actually a trial that involves 5,000 individuals in 45 centers around the country to determine the effectiveness. This really will eventually get to the area of precision medicine.

The second thing for those people who are sort of underneath the iceberg, the 86 million Americans who have a possibility of going on to develop diabetes, we have tried to translate a very effective Diabetes Prevention Program to scale this up in a way, to offer this lifestyle, which was quite effective in these patients, to prevent them or delay them from becoming a diabetic.

These will have an important financial role in the future, in terms of cutting costs.

Senator BLUNT. Thank you, Mr. Chairman.

Senator Mikulski.

Senator MIKULSKI. Mr. Chairman, thank you so much for organizing this hearing.

To our colleagues from NIH, this is the committee and the members here today are the pragmatists. When you look at us, we have a chairman who is very much dedicated to NIH, certainly a vice chairman who is. We have the authorizers here in terms of Murray and Alexander.

All of us here have a history of support for this, so you have people who really want to be nonpartisan. So I want you to know that.

Dr. COLLINS. Thank you.

NIH WISH LIST

Senator MIKULSKI. We are stymied by our own processes. When I first arrived in the Senate, we had a triad that worked. Authorizing would often create great policy on a bipartisan basis, Kennedy-Hatch, Kennedy-Kassebaum, et cetera. We had appropriations that really could move the ball forward. And we had a budget process that gave us an orderly methodology process for doing that.

So we have problems here. So we have big problems here. I know that you live them out every single day.

Colleagues, when I visit the National Institutes of Health, which has been my great joy to represent for 28 years, I call it the "National Institutes of Hope." This is what we just heard here, the National Institutes of Hope, in both what they do on the campus in Bethesda, but also what they do through the great extramural research like at the University of Maryland and Johns Hopkins.

Dr. Lorsch, you are a Hopkins guy. They are going to dedicate a room the Hopkins Club, the faculty club, 2 weeks from now. Thirty-eight people associated with Hopkins have won the Nobel Prize, two-thirds of that have been in life sciences—38 people, one university—but because of the role that our government plays in doing that.

But we are an economic engine. When you think about the jobs that are created because of you in pharmaceuticals, biomedical, medical devices. You are a turbo engine.

So rather than seeing you as a cost factor, we should see you as an economic generator. And I hope that we can be able to do that.

I am deeply concerned about the caps. I do not like budget caps. Most of all, I don't like the caps on innovation. We cannot continue to cap innovation. We cannot cap breakthroughs. We cannot cap the opportunity for young people to dream for these careers like Dr. Rosenberg and all of you have here.

So here is my question to you. When we look at both the research to be done and the workforce that needs to do it, I worry about the young investigator and the debt that they carry that is a deterrent to pursuing this.

Could you tell me, if we could go down the table, if we lifted the caps and went to President Obama's budget, nothing more, President Obama's budget, what would be the three things each and every one of you could do? And also, how would it impact young investigators?

Dr. COLLINS. Okay, folks, there is the challenge. Maybe we should just quickly go down the table.

Nora, do you want to kick this off?

Dr. VOLKOW. You want three of them?

Senator MIKULSKI. If you just have one, one would be enough.

NIDA

Dr. VOLKOW. No, no. Number one is we would accelerate the development of medication for addiction. There are many very interesting potential targets. But since the pharmaceutical industry is not investing, that responsibility relies in the Federal Government money, predominantly through the NIH. So that would be one.

The second one would be to expand the study to understand how drugs affect the development of the human brain. We now have that technology. We should have that information. That will inform prevention efforts.

The third one will relate to actually making research careers more accessible to the young investigators so that we do not lose talent.

NIDDK

Dr. RODGERS. I would just expand upon that. I would say that the three areas that I would focus on are the young investigators. We know that there are two critical points in which an investigator is likely to stay in research or exit. One is on their first application to get a grant. The second is getting that renewed. If they get through that second hurdle, it is likely that they are going to be with us a long time. So we would like to encourage them by making incentives for both the first application, as well as the first renewal.

The other point that I would make is that with expanded funds, we would be able to allow for expansion of some of our existing clinical studies, which are very expensive, because of the curtail that we would have to do. One way to amplify the investment in infrastructure in these clinical trials is by having ancillary studies to these trials. So I would expand existing trials, as well as ancillary studies to these trials.

NCI

Dr. LOWY. Thank you, Senator Mikulski. In the question of young people, we at NCI are in the process of trying to develop new approaches to enhance their ability to move from being graduate students and postdoctoral fellows to starting their own laboratories. The areas where we would invest would be in cancer prevention, cancer screening, and cancer treatment, using molecular precision medicine approaches, which have enormous potential in those areas.

I would highlight the potential of immunotherapy, as was discussed earlier, because of the issue of its potential for improved responses, decreased side effects, and scalability, as Senator Blunt mentioned.

NINDS

Dr. KOROSHETZ. In terms of research projects, we talked about the BRAIN Initiative. There is also the National Action Plan for Alzheimer's Disease Research. Both of those have milestones. It is all planned out. If we had the funding, we could really accelerate both of those major projects.

In terms of young people, I think supporting young investigators is incredibly important. The average age of becoming independent with an NIH grant is now going to the mid-40s. We have to move that down. We have a couple of things that we are considering at NINDS to support somebody who is really young, who really looks bright, and just give them a chance much, much earlier in their career.

NIGMS

Dr. LORSCH. My institute mostly funds fundamental basic research. The great ideas that lead to the discoveries that Dr. Collins told you about in basic research do not come from me and, as much as I esteem my colleagues, do not come from them. They come from the great brilliant minds at the universities, institutions in your districts across the country. We would focus on supporting investigator-initiated research to promote these brilliant scientists to do their work.

As a measure of that, and the success of my Institute, as Dr. Collins alluded to, has funded a number of Nobel Prizes. I would have said 81 yesterday, but as of this morning, it is now 83. I think that is an indication of the power of investigator-initiated research.

We would certainly have a focus on promoting the careers of the young scientists who will win the Nobel Prizes of the future.

Senator BLUNT. I will point out that only Senator Mikulski gets 50 percent more time than she is allocated. That is totally fine with me.

One of the things I did want to do today was get on the record the kinds of things you would do now. Strictly speaking, to Senator Mikulski's question, the President asked for half of the increase that the Committee has proposed that you get. So I am going to look very carefully at all the things you said you would do if you had the President's number, and assume I can multiply that by

two, and those will be the things you would do if you had the number the Committee is proposing that you get at NIH.

Mr. Shelby.

Senator SHELBY. Thank you.

$3 BILLION INCREASE?

Dr. Collins, picking up on what Senator Blunt said, talking about money, funding, which is important, say you had $3 billion more, above, what could you do with it, as far as investigating and hoping to turn a lot of the investigative results into better health and better treatment? What would $3 billion—just use that. I made it up, but I hope we could do something for you. What would it do for you? What would it do for us, everybody?

Dr. COLLINS. Yes, what would it do for America, for the world? Senator, I appreciate the question. It is a lovely thing to contemplate. As you have heard, we have lost over the last 12 years, about 22 percent of our purchasing power.

This would be about a 10 percent increase. It would not quite get us back to where we were in 2003, but, oh my gosh, it would be an enormous shot in the arm to a community that has such talent and such energy and is basically being squeezed to the point that a lot of innovation that we could be doing is just not happening.

You heard from my colleagues the areas they would pick from their own particular domains. I am sitting here thinking about the other institute directors who are not here. I will mention a couple others that I would want to put on that short list, that if they were here they might speak to.

Vaccines, I mean, we are on the brink of being able to develop a vaccine that would work against all influenza strains. If Dr. Fauci was here, he would tell you all about that. We have a path toward something that would result in not needing your yearly flu shot that has to be re-engineered every year, and sometimes it works and sometimes it does not, but maybe more importantly protecting against that next worldwide pandemic, which is overdue. We are not pushing that as hard as we should because the resources simply are not there.

Vaccine for HIV/AIDS, we really do now see a path to make that happen after 30 very frustrating years. Yet, we can't go as fast on that as we would because the resources are unavailable.

The Precision Medicine Initiative, which we hope to start in fiscal year 2016, which I think has a lot of bipartisan support and which the scientific community, after many workshops and a working group that debated about this, is very jazzed about. We cannot start that if we have a yearlong CR, as I said previously, in answer to Senator Murray. But we could start it, and we could ramp it up much faster if we had this kind of curve to work with as far as research.

Then there is this whole area that we call high-risk, high-reward research. We just announced, a couple days ago, the funding of about 78 of these new awards. These are pioneer awards, new innovators, early independence, and transformative awards. These are NIH awards where you cannot apply unless you have an idea that is really out-of-the-box. And you do not have to have a lot of preliminary data, if your idea is exciting, we want to see what you

could do. Give the awardee the money and let them run with it. Many of the institutes are taking that tack, but we could go faster and could inspire people to be more risk-taking, if we had that kind of opportunity.

Put all that together and with $3 billion, let's try it. Let's try the experiment and see how that turns out. I promise you, it would be amazing.

Senator SHELBY. Also, not only health, it would be a good economic investment in our country.

Dr. COLLINS. Thank you, Senator. The repeated economic analyses demonstrate the return on investment for dollars that go to NIH is about 2.2-fold in the first year to the local community. And of course, our dollars go out to all 50 States.

UPDATE ON AUTOIMMUNE DISEASES

Senator SHELBY. I would like to touch quickly on, where are we today as far as cutting-edge research on cystic fibrosis and also a lot of the autoimmune diseases, such as lupus.

Dr. COLLINS. Well, thank you again. Great questions and great progress being made in that space. I have a personal, deep, and longstanding interest in cystic fibrosis, as my own laboratory found the cause of that back in 1989 when I was at the University of Michigan.

This is a very exciting time for that disorder because after all those years of figuring out how that small glitch in the genome was capable of causing this disease, we now know a great deal about the protein that is normally made and why it does not do what it is supposed to in cystic fibrosis.

Just in the last few months, we have now seen the second drug strategy approved by the FDA for the treatment of more than half of those with cystic fibrosis based upon a small molecule, a drug that is based upon molecular understanding of the disease. Very exciting times, indeed.

I just want to mention one very exciting public-private partnership, the Accelerating Medicines Partnership, which several of us have been working very hard to bring together 10 drug companies with NIH to work together. And one of the targets is, in fact, lupus and rheumatoid arthritis.

Again, I showed that picture about T cells. What is going on with T cells and lupus? Are they overactive? Are they going after normal tissue when they should not? What can we do with the new technologies to understand how single cells are behaving in order to come up with strategies that work better than what we currently have?

So all of these areas are just full of potential right now.

Senator BLUNT. Thank you, Senator.

Senator Durbin.

Senator DURBIN. Thanks, Mr. Chairman. Thank you all for being here.

Let me just say at the outset, to address this side of the room for a moment, gathered in this room at this moment in the United States Senate are the 11 or 12 people who could literally make a difference for generations in medical research, as was noted by Senator Mikulski. We have both the authorizing committee and the

appropriating committee in the Senate. If we took a stand, a bipartisan stand, on medical research and said, come hell or high water, we are not going to tolerate a shutdown, a sequestration, a CR. We are going to increase the funding for NIH and related medical research agencies. We can make a difference.

We can make it clear, do not try to get through the Senate, if you are going to touch it.

I want to commend the chairman, because I bothered him, begged him, challenged him for a long, long time, based on Dr. Collin's admonition to me: Give me 5 percent real growth for 10 years, and I will light up the scoreboard.

We have done it in this bill. I might add, parenthetically, at the expense of some other things that are equally important, I should say, as well.

But I want to commend the chairman for making this commitment for 7 percent growth at NIH, which includes 5 percent real growth at NIH. And as you said, and was asked by Senator Shelby, a onetime infusion is a good thing, but constancy, predictability, is what leads to researcher commitments and long-term success in what we achieve.

I would like just to throw out as a possibility that we rally around one particular person who is up here.

For 28 years, Barbara Mikulski has been the strongest voice for the National Institutes of Health on Capitol Hill. She is leaving soon, unfortunately, for all of us. But I hope we can make a Mikulski promise that we are not going to forget the commitment of this budget and the commitment in years to come.

And I will tell you this, in the time I have been in the Senate, you do not want to break a promise to Barbara Mikulski. It is something you will hear about.

Senator MIKULSKI. Well-said.

UNDERSTANDING ALZHEIMER'S

Senator DURBIN. So I hope we can be inspired by that.

Let me try to bring this down to the ground level, if I can. I have two questions, if I can get to them.

The first is, when we talk about $2 billion in growth, $2 billion in growth in this coming year, I need to ask you, when it comes to areas like Alzheimer's, we know that we spent $154 billion on Alzheimer's treatment, just Medicare and Medicaid. We estimate that the private contribution of families is almost equal to that in value. So we are talking about one-half of 1 percent of what we are spending as a Nation on Alzheimer's as the delta, the $2 billion that we are looking for here.

When it comes to brain research, we now have reached I think a point, please confirm if I am right, where we can start to visualize the development of Alzheimer's in the brain and know many years before the obvious onset that a person is moving in that direction.

What do you see, Dr. Collins, or those who are here with you, in terms of what we could do if we knew 15 years in advance that Alzheimer's was likely to occur? What could we look forward to do soon to delay it or, God willing, find a cure?

Dr. COLLINS. So, I am showing you a picture that outlines the statistics. I did not know you were going to ask the question, but you can see what the relative numbers are here in terms of what is currently being spent on Alzheimer's disease. These are 2013 numbers. Obviously, that number is now going up, and we need it to. But comparing that to what we are spending, $203 billion in 2013, and an estimated $1.2 trillion in 2050, if nothing gets done.

So, this is a matter of great urgency, not just because of the economics, of course, but also because of the enormous human tragedies that are attached to this disease.

Dr. Koroshetz, as a neurologist, Director of NINDS, can tell you something about where we are on this and why we are optimistic that we can actually get to a place that does not result in that enormous blue arrow.

Dr. KOROSHETZ. Yes, thanks, Senator. I think you made a really interesting point, that for the first time, we can actually see what is going on in the brain in people with Alzheimer's disease. In the past, we knew what happened when people died, but we really could not see brain changes happening in living people. But now, we have brain imaging markers for amyloid and tau, which are the major culprits in Alzheimer's disease. We can see that in the brain now of living people.

As you said, we can see amyloid developing years before the tau starts to set in. The tau seems to be the thing that kills the cells. So Alzheimer's is like the gun. Tau is like the bullet.

So the vision is that we develop a screening tool for people who are developing the amyloid, determine if they are going to develop Alzheimer's, and then come in with a drug to block that process.

In fact, those drugs are currently being tested in clinical trials. So we could get lucky. I mean, this looks very, very promising, at this point in time.

Senator DURBIN. And let me add, because Secretary Ernest Moniz would hope that I would add, that this technology, which allows us to visualize, our Department of Energy and Office of Science had a lot to do with this.

So when you talk about medical research, the technology side of this equation relies on other agencies.

Do I have 10 seconds? Darn it. I will try to be here for the second round.

Dr. COLLINS. I would like to just quickly say that that is a very good point. We actually have a joint meeting about the brain between the Department of Energy and the NIH coming up in 2 weeks in Chicago.

Senator BLUNT. Senator Alexander.

Senator ALEXANDER. Thanks, Mr. Chairman.

I am sorry Senator Mikulski left because I would like for her to know that Dr. Collins played the guitar and sang at a place that Senator Durbin has been and Senator Mikulski desires to go, which is the Bluebird Cafe in Nashville. It was quite a show.

What is that song? Knock Out Disease?

Dr. COLLINS. That was it. I am surprised that you remember. I thought you might have suppressed the whole thing.

ADMINISTRATIVE BURDEN

Senator ALEXANDER. It is a great hit.

I mean, we all admire your work, but we also admire the work of your team. We know they could be making more money some other place, but the fact that they are here and working to help other people is something we all respect and appreciate.

I asked you, Dr. Collins, earlier about the bill that Senator Murray mentioned she and I are working on. We are trying to create an environment where precision medicine can succeed, where we get inventions and discoveries through the process more rapidly.

One of the problems we have is that the National Academies groups have identified that investigators, the ones that we are wanting to get more money for, spend 42 percent of their time on administrative tasks. Now, if we are talking about millions more for investigators, shouldn't we be spending an equal amount of time trying to get that 42 percent down, so we create more dollars there?

There is a new report headed by the former president of the University of Texas at Austin, which makes a number of serious specific recommendations about how to deal with that. One of them includes a research board that would coordinate an approach towards the regulations and policies that effect researchers that received the $40 billion we put out, not all of that through NIH, but to colleges and universities to try to eliminate duplication and make it more efficient.

My question is, and you do not have to do it today, a lot of their recommendations have to do with NIH, will you review that report, and over the next year set up a systematic way to consider making the changes that it makes? And if you have impediments either within the administration or the law that would keep you from doing that, if you could let us know, we might be able to include them in the legislation Senator Murray and I are working on.

Dr. COLLINS. Senator, I appreciate very much the role you played in bringing this important issue to the attention of the academic community and other constituents as well, including the government.

Senator ALEXANDER. Thank you. I am going to ask you to leave me about 2 minutes, because I have another question I want to ask.

Dr. COLLINS. We will take with great seriousness this report. We have looked at it in a preliminary way. We will look at it much more deeply. I think we do have a number of ideas and responses to that. I will be glad to share with you about how we could do something to reduce that 42 percent.

BEST FUNDING MECHANISMS

Senator ALEXANDER. Thank you. I want to ask you some questions about funding, but I do not need the answers today. But I think all of us need the answers in the next few weeks.

The House included something called mandatory funding as well as discretionary funding. For many of us, mandatory funding is the villain. The reason you don't have money is because that part of

the budget has gone up like this, and the discretionary side is like this, and you are on the discretionary side.

So our visceral reaction is against any new mandatory funding. But I am convinced that this is a critical time in science and a critical time of opportunity, so I am willing to think about that. I have these questions, as I think about that. These are the questions I would like to talk with you about some time.

What happens at the end of the 5 years that the House proposed? There is a cliff, and you lose $2 billion. What happens then?

What is the purpose of the mandatory funding? If there is a difference between discretionary funding and mandatory funding, do you just mix it all up or is there some distinct purpose that would justify a steadier stream of money toward mandatory funding? What would that be?

Should there be a focus for the mandatory funding on preventive medicine, for example? Or on precision medicine, for example? Or on investigators, for example?

And what about oversight? We had an embarrassing thing happen in the NIH about its manufacturing of sterile drugs recently. If you are not accountable to us for what happens there, then you are not accountable to anybody, really. That is our job as appropriators.

So as a Republican, when I read Ben Bernanke's column that says that the Fed cannot create a growth economy, it takes education, capital formation, infrastructure, and research and technology, I agree with that. I am all for more research. I think we should be doubling energy research, rather than subsidizing windmills and putting money in the pockets of rich investors somewhere for after 22 or 23 years.

I think we should be setting priorities. My priorities do include your work and Dr. Moniz's work. But I would like you to think about the questions I asked about that type of funding and maybe one of these days we will have a chance to talk about it.

Dr. COLLINS. I will certainly do so.

Senator BLUNT. Thank you, Senator.

Senator Merkley.

YOUNG INVESTIGATORS

Senator MERKLEY. Thank you very much, Mr. Chairman.

And thank you, Dr. Collins, and your team, for the vision. The video of the T cells destroying the cancer cells is inspiring. I think we're all thinking that we hope that over the years ahead every possible type of receptor on every possible type of cancer cell and the ability to program T cells to attack them will continue to develop. I think that is the vision that we are anticipating.

One of the concerns that I have heard often, and Oregon Health Sciences University is a major research partner with NIH, a lot of grant funding goes there, is the stranding of young researchers.

Dr. Rodgers, I believe you mentioned the young investigators, folks who are partway into their career. They have gone through their postgraduate work. They are in a laboratory, and then the grants don't come through, and then they have this incredible specialty about some form of nerve communication or chemistry deep

within the cell that may be the key, but who knows. But suddenly they are going, "Well, what do I do now?"

Does this continue to be a problem? And to what degree should we be deeply concerned about this loss? We spend a huge amount of resources to develop that talent and then suddenly its ability to be applied is cut short.

Dr. COLLINS. Well, I think we should be deeply concerned. We do put a great deal of resources into the training of this generation of young scientists. The talents and skills that they possess are incredibly impressive.

And yet, if you, as I often do, go and visit universities across this country and meet with graduate students, postdoctoral fellows, it used to be when I made those visits, they wanted to tell me about the science they are doing. Now they want to tell me about their anxiety about whether there is a career path for them or not, or whether they ought to think about doing something else. And some of them have decided to do other things or have gone to other countries where, in fact, the support for biomedical research is continuing to grow even as ours has been shrinking.

Every Institute at NIH thinks about this, worries about this. We sit around tables together and try to figure out strategies.

Maybe I will ask Dr. Lorsch, because his Institute is deeply engaged in our training programs, to say something about some of the ideas we are pursuing, although I will tell you there is no magic here without seeing some relief from the budget squeeze in terms of what we can do. We can try to make every dollar count.

Senator MERKLEY. Thank you. I would ask you, Dr. Lorsch, to be very brief because I have two more questions I want to get to.

Dr. LORSCH. Sure, I will be very quick. We are starting a new pilot program to explore a new grant mechanism. There will be a single grant per researcher that would actually address some of Senator Alexander's issues about administrative burden, but it would also be more stable for the investigators because it would be a single grant. As Dr. Rodgers alluded to, this would help carry them through that sort of valley of death after their first grant when the second grant renewal is very hard. That is something which has our main focuse.

Senator MERKLEY. Thank you.

SEQUENCING

I want to go back to where it started in terms of the receptors and the T cells. Earlier in the DNA world that you were centrally positioned in, it took an enormous amount of time to do sequencing. Now that is probably, I don't know, 1/10,000 of the time? I am not sure what the factor is, but it is just a very tiny fraction.

Do you see a similar curve in terms of the time and effort it takes to identify T receptors and be able to produce T cells in a way that can attack specific cancers?

Dr. COLLINS. Yes. It was 13 years for the first human genome. You can now get yours sequenced in a day or a little less, so whatever that factor is.

In terms of looking at proteins, of course they are encoded by genes, so we have a connection there, where we can take full advantage of what we have learned all through the last several dec-

ades of recombinant DNA. So we have a pretty good sense of what in fact are the proteins that are on the surface of various cells, including cancer cells.

The trick is that every cancer is a little different. This is where precision medicine part of this fits in. That is very much, I think, at the cutting edge of trying to bring immunology, genetics, genomics, and cancer biology together to figure out how to make that strategy work not in a one-size-fits-all, because it probably won't work that way, but in a precision, individualized way.

E-CIGARETTES

Senator MERKLEY. Shifting topics completely in the last 30 seconds here, e-cigarettes, we have seen a tremendous growth. There have been studies that NIH has funded about the high school students tripling their use in a single year, and so forth.

What do you see as the role of NIH in terms of this new form of tobacco and tobacco addiction?

Dr. LOWY. Thank you, Senator. The NIH is concerned about tobacco consumption because it has such an impact on disease. And in addition, the issue of e-cigarettes where we do not know what either the short-term or long-term impact is from the cigarettes themselves, nor do we know what the implications are for behavior. Therefore, the NIH, in conjunction with the FDA, is conducting research to investigate these critically important areas.

Senator MERKLEY. Thank you very much.

Senator BLUNT. Thank you, Senator.

Senator Cassidy.

FUNDING DECISIONS

Senator CASSIDY. Hey, doctors, thank you all so much. As a practicing physician sometimes still, I am so aware of your good work. I think we should double your budget, because I understand the impact that would have upon my patients, among which, when I did my residency in 1983 in Los Angeles, the epicenter of HIV, at least the Western epicenter, I am very aware what was formerly a death sentence is now something you live with.

Let me ask, because, Dr. Collins, you know that I have been concerned that 20 years ago I think it was GAO or IOM suggested that NIH rebalance its HIV spending from the 10 percent it had become to diseases such as Alzheimer's and dementia, which are more important now.

If you receive the 7 percent increase that the chair and the ranking member aspire for, we all do, will 10 percent of that budget continue to go, or roughly 9.5 percent, 10 percent, of that, will that go to HIV research?

Dr. COLLINS. Senator, you and I have discussed this on occasion, and I think you are raising a good point about whether it makes sense to have a formula-driven way in which we define how resources are to be spent, or should we focus that entirely on what the public health needs are and what the scientific opportunities are, the things that NIH usually does.

No, I do not think that if we had the wonderful good fortune to receive this kind of increase, that there ought to be a lockstep 10 percent formula-driven basis upon which we define the HIV/AIDS

research budget. I do think we should not take our foot off the accelerator at a time when HIV/AIDS is poised I think for some major advances, including the potential development of a vaccine. So I think we should step away from the formula.

Senator CASSIDY. And I do not mean to interrupt. I just have such limited time.

Dr. COLLINS. Sure.

Senator CASSIDY. In your directive, I do not have it in front of me, but you mentioned among the focal points in terms of the HIV research would be an emphasis upon comorbidities.

Dr. COLLINS. Yes.

Senator CASSIDY. Now when we hear from Merkley and Blunt and others about young researchers not having dollars, this is a concern to me. We pulled the minutes from the 2013 National Institute of Heart, Lung, Blood. They are speaking about how the success rate of non-AIDS applications are 18 percent, but for AIDS applications, they are 42 percent, meaning that it took a less quality project to be approved. And they hope to encourage more submissions of AIDS projects and hope to understand the barriers to submission.

Then I see the project currently being done is looking at the cardiovascular comorbidities in HIV, along the lines of that which have proposed. And yet then we find out—I think we found out that of the 610,000 people who die every year from heart disease, only roughly 1,800 of them have HIV as a determinative cause.

But nonetheless the money we're spending on this study is 21 percent of the budget of the National Heart, Lung, Blood Institute. So we're spending 21 percent of a budget for 0.29 percent of those who die from HIV.

Now if we are going to focus on comorbidities, spending 21 percent of the institute's budget on the 0.29 percent who happened to be co-infected with HIV, it seems like we're going in the wrong direction.

Thoughts?

Dr. COLLINS. So, I am not totally familiar with the detailed numbers you present, but I will certainly look at those.

Certainly, we are in the process, Senator, of trying to right-size the way in which our HIV research budget is being allocated. The Office of AIDS Research has the potential to move dollars around between Institutes and between programs.

Senator CASSIDY. But can we move it out of HIV? For example, I have a study here. There has been $1 million that has gone to study behavior of Chinese men having sex with men in some city in China, $1 million over the last 4 years. It would have been great to put that to Alzheimer's or to Oregon, where Merkley's researcher would find—one of your predecessors said that we are not the international institute of health, we are the national institute of health.

Why are we spending 1 million bucks on a behavioral health study in China?

Dr. COLLINS. Again, we have now identified I think the four areas of high priority. Frankly, I do not think that that study would necessarily fit those priorities.

Senator CASSIDY. So I guess my question, you mentioned the Office of AIDS Research moving dollars between Institutes. But if this is the kind of study—if at NHLBI, its 42 percent approval rate for the HIV/AIDS study, frankly, they are getting too much money for HIV/AIDS. They are having to find people to apply for something which is 21 percent of their budget.

Can we move money out of that area into neurodegenerative diseases, Alzheimer's, Parkinson's, ALS?

Dr. COLLINS. I certainly agree with you that we should be making decisions across NIH on the basis of public health needs, scientific priority. I would say there are scientific priorities emerging in HIV/AIDS that I would not want to see neglected, particularly the opportunity to end this epidemic, and particularly the investment in the vaccine, which is likely to be quite expensive.

So taking your point, I do not think we should in the process of rethinking this portfolio, which we are doing actually quite actively right now, we should not neglect the potential of actually investing in different ways in HIV/AIDS that will bring an end to this epidemic.

Senator CASSIDY. There is something else I have read, and I will close with this, and I have read so much about this, I lost this quote. But if you decide to focus exclusively on the cure of one disease, inevitably, you end up ignoring other more pressing needs.

We are spending $600 million right now on AIDS vaccine domestically, and I think $24 million on the international AIDS vaccine initiative, not that we couldn't spend more, but to justify 10 percent of the budget on the basis of that seems as if we will end up neglecting Alzheimer's, dementia, mental health, addiction, et cetera.

I yield back.

Senator BLUNT. Thank you, Senator.

Just for the record, Dr. Collins, you may have mentioned, but I don't know that I heard it, if you did, the four target areas in HIV/AIDS research, when did you announce that? That was a recent reevaluation of where you are headed and a recent announcement?

Dr. COLLINS. It was in August, Senator. I can quickly say those four priorities: reducing the incidence of HIV/AIDS; research towards a cure for those who are infected who otherwise are doomed to lifelong treatment; a next-generation of therapies with better adherence and fewer side effects; and these HIV-associated comorbidities, recognizing there are many, many thousands of people already infected who are having some of those comorbidities. We need to understand them better.

Senator BLUNT. Thank you.

Senator Capito.

IDEA PROGRAM

Senator Capito: Thank you, Mr. Chairman.

I thank all of you on the panel.

I would like to thank Dr. Lorsch for coming and spending time in West Virginia at West Virginia University, talking about a program that I learned so much about, the IDeA Program, which is a smart, successful program. So I thank you for that. There is research with stroke and brain, and also a collaborative effort with

other universities, Marshall University, West Liberty, and Wheeling Jesuit. So I thank you for that.

I wanted to give you a chance to say if you had any takeaways from the visit there that you might be able to address.

Dr. LORSCH. I want to thank you again, Senator. It was a fantastic visit that really energized my staff and myself.

One thing we noticed consistently about the IDeA Program is that it is full of best practices. I think we really saw two there.

The first, as you mentioned, was sharing resources to create economies of scale, particularly in access to technologies, which we saw was very critical, especially for the young researchers. I think that model of creating economies of scale through sharing technology resources is something we should think about moving nationally because it can really get the taxpayers more science done for their money.

The other area is training young investigators. We saw how the COBRE program, the Centers of Biomedical Research Excellence, focuses on training young investigators. There was recently a paper, just last week, published by a group in Nevada, showing that investigators who participated in the COBRE centers were three times more likely to succeed than investigators who did not participate in the COBRE centers, a matched set of investigators in terms of getting R01 grants and publishing papers.

Again, I think given the importance of young investigators, taking that model from the IDeA Program and thinking about how we can use it nationally is really important. I certainly give Senator Cochran a lot of credit for developing the IDeA Program in the first place.

So thank you again.

DIVERSITY IN CLINICAL TRIALS

Senator CAPITO. I think the enthusiasm we saw with the young investigators, the young researchers, is something that was very inspiring for me. I have heard a lot about the problems of them moving to the next steps, so hopefully we can determine that.

Dr. Koroshetz, the National Institute of Aging is partnered with the Centers for Disease Control and Prevention and the Administration of Community Living in an initiative to bring more older Americans into research programs. The program has specific focus on Alzheimer's patients.

Both my parents recently passed away from Alzheimer's. Can you talk to somebody like me who is 60 years old? How do you get into these programs? How expansive are they? What are your expectations?

And, actually, I went to an Alzheimer's meeting just the other day, and they were talking about the push for diversity in your research, where you are researching minorities and other ethnic groups, women, men, because it manifests itself differently, possibly in different types of groups, so that is a big question for a little bit of time.

Dr. KOROSHETZ. Sure. Well, the National Institute of Neurological Disorders and Stroke and the National Institute on Aging, which is the point institute for Alzheimer's disease at NIH, are really working very hard on Alzheimer's projects.

I think, as you mentioned, one of the stumbling blocks is the culture of research in this country. So as we develop new therapies, our barrier is really the number of people that we can enroll in studies. The National Plan to Address Alzheimer's Disease has a number of milestones, which are trying to really expand to increase enrollment.

So in cancer, for instance, a large percentage of patients with cancer will enroll into a trial. For neurological disorders, it is much lower. So we really need to push on that. I think we have some really good plans to do that.

PRESCRIPTION DRUG ABUSE

Senator CAPITO. I would like to help you with that, because I think also it goes undiagnosed or it's, "Well, they are getting old, and that is just sort of the way it is." I am really excited to hear about what you talked about with the possibility of a vaccination or vaccine or something.

Quickly, Dr. Volkow, I am from Appalachia, West Virginia. We have a very high incidence of prescription drug abuse and now heroin just on an astronomical rise, overdoses and deaths resulting from the use of heroin.

I am glad to see that you wrote in the Huffington Post, which is something I don't read very often, I will admit, to embrace the concept of addiction as a chronic disease. I think we are all with you there. I do not think one of us probably has been untouched by this.

Rural America is really suffering from this. Some of the smaller States, lower socioeconomics, they are going to heroin, and in other high unemployment areas.

Where do you see your role here?

Dr. VOLKOW. The urgency and the tragedy of what is going on around the country, and in the Appalachia region, has made this one of our priority initiatives. It is also one of the priority initiatives for HHS.

So we have been working with our sister agencies or brother agencies to actually integrate our projects to maximize the likelihood of success. So HHS has three items, one of them is better prescription practices for the proper management of pain. NIDA, for example, is very invested in developing alternative therapy treatments for the management of pain because we are very restricted by what we currently have, which has resulted in the overreliance on opiates, item number one.

Item number two, greater access to naloxone, which basically is a medication that overturns——

Senator CAPITO. Right, that was just legalized in our State.

Dr. VOLKOW. Which is wonderful.

So we are partnering with pharmaceuticals to develop alternative ways of administering naloxone that do not require an injection, so anyone can administer it.

The third one is deploying medication-assisted therapies that actually have been shown to prevent overdoses and prevent HIV infections. So we are developing alternative medications that can increase compliance, so we are already doing that.

What we want to do is to partner with CDC in order to develop a project that can target the Appalachian region. I visited the place, and I was struck by how minimal the infrastructure there was in some of these towns. So the issue is how does one address this? We have tools. How do we deploy them?

Senator CAPITO. Right. Thank you.

Thank you very much.

Senator BLUNT. Senator Moran.

ALZHEIMER'S RESEARCH FUNDING

Senator MORAN. Mr. Chairman, thank you very much.

Dr. Collins and crew, welcome. Thank you for the opportunity to have a conversation today.

Dr. Collins, NIH recently released its professional judgment budget for Alzheimer's. Am I correct in assuming that the President's budget request was the starting point, that you are going to build upon the President's request? Is that true?

Dr. COLLINS. That's true. We were building for fiscal year 2017 what a professional judgment would look like, assuming that the President's budget was the fiscal year 2016 number.

Senator MORAN. I want to give you the chance to tell us, if we are successful in accomplishing what this Committee did in regard to increases in funding over the President's request, would it give us a greater opportunity to advance the success, the research necessary to address the issues of Alzheimer's?

Dr. COLLINS. Yes, Senator, it would. Because of some of the things we imagined that we would fund in fiscal year 2017 could, in fact, be started earlier in 2016, so we would want to revise the number for the fiscal year 2017 professional judgment budget on that basis.

Senator MORAN. So Senator Blunt's subcommittee and the inclusion of a $2 billion increase at NIH, plus the specific issues related to brain and Alzheimer's, would have a significant consequence on the ability to advance the cause, elimination, cure, treatment?

Dr. COLLINS. I think we are not limited at the present time by ideas or talent. We are limited by resources. Certainly, if it were possible to have more resources in 2016, we could start projects that would otherwise have to wait longer. So, yes, we could go faster.

Senator MORAN. Of course, Dr. Collins, I think you are a very bright, intelligent person, but I have discovered that you also have the ability to say the same thing more than once. Perhaps you should be a Senator. Dr. Koroshetz.

Dr. KOROSHETZ. I would just say, to go with what Francis said, for the Alzheimer's plan and for the BRAIN Initiative as well, we have serial projects in which one depends on the other, and we do not know what fiscal year 2016 will do, but we are ready to go. We have announcements ready but we will not be able to fund them unless additional money does come.

Senator MORAN. So, let me make sure I understand that. You are prepared to expend the dollars that are included in the Senate Appropriations Committee recommendations, our appropriation bill?

Dr. KOROSHETZ. We are shovel ready.

Senator MORAN. Good to hear.

The Alzheimer's Disease Research Summit occurred last February. NIH is poised to revise the research milestones that it created in that national plan. When can we expect that?

Dr. KOROSHETZ. So, the National Plan to Address Alzheimer's Disease is actually a community plan that was developed with consultation from the scientific community, advocacy community, patient community, and the caregiver community. NIH conducts regular revisits to the search recommendations and milestone referenced in the plan, so it is revised on a regular timeline. We alternate between NINDS, which covers Alzheimer's disease-related dementias (like vascular disease that causes dementia, Parkinson's disease that causes dementia) and the NIA, which leads the Alzheimer's focused research milestones.

So, on a regular basis, we are alternating between those two areas and revising the milestones.

Senator MORAN. Thank you very much.

Dr. Collins, in the budget hearing back in April, you and I had a conversation in which you testified something along these lines, "To achieve our mission, we must serve as effective and efficient stewards of the resources we have been given by the American public." This is continuing to quote you, "To support this focus on priority-setting, we are developing an overarching NIH strategic plan, and will be linking this with individual Institutes and Centers strategic plans that reflect the rapid current progress in bioscience."

My question is, what are the details? Fill in the spaces about what has transpired since that conversation occurred. What are you doing that is new and that will mean that we are going forward, and we have latest opportunities because of that efficiency to achieve more?

Dr. COLLINS. Well, we are working very hard on developing the strategic plan that you mention. We are scheduled to deliver that to Congress in mid-December. It does try to lay out in a clear fashion across all of NIH how it is that we set priorities; how we make decisions about where the dollars are most efficiently spent; and also how we are being good stewards in terms of how the process of peer review and council review and director actions on what we fund is carried out, as well as a number of other efficiencies that we are concerned about, including what Senator Alexander was discussing earlier, just in terms of the burden that is applied to investigators who are trying to get the research done, as well as human subjects oversight and so on.

There will be a lot in this document that will lay out, I think, in greater detail than has been possible before how we intend to use all the dollars we have for the best benefit.

Senator MORAN. Mr. Chairman, Dr. Collins, let me repeat myself. I have offered this admonition, if that is a safe thing to say, that we are often told as Members of Congress that we do not want to be meddling in the "politics of deciding where research dollars should be spent." I share that view, but it means it is incumbent on NIH to make the decisions that are necessary as to where the dollars spent are the most likely to achieve the quickest, the fastest, the best, the necessary results.

Dr. COLLINS. And I welcome that responsibility, as do all of my colleagues.

Senator MORAN. And I apologize if I offended you for suggesting that you could serve in the United States Senate.

Senator BLUNT. There might have been a time when that would be considered a compliment, but it probably would not be right now.

We do have time for a second round of questions. We will start with Senator Murray.

PREVENTING TYPE 2 DIABETES

Senator MURRAY. Thank you very much.

Dr. Rodgers, I wanted to go back to you. You spoke earlier about the 29 million Americans who have diabetes, and the 86 million who are prediabetic. That sounds to me like we have a crisis on our hands, as the number of Americans with that disease continues to grow.

You mentioned the work your Institute has done on prevention programs that incorporate regular exercise and reduce fat intake and the huge difference it makes. The CDC's chronic disease program, which our bill has regrettably been forced to cut, helped fund programs like one in my home State that supported community health efforts through the YMCA and some other local organizations that promote healthier living.

What might taking that preventative program to scale mean for this country's diabetic epidemic?

Dr. RODGERS. Thank you, Senator, for that question.

The YMCA that you are referring to, was able to develop what we did in the clinical trial for the Diabetes Prevention Program, which is a lifestyle intervention on an individual basis, scale it up by doing the same lifestyle intervention but providing it in a group setting. In fact, their results after the first year or 2 were quite similar to what we achieved in the individual program, in terms of weight loss, et cetera.

But more interestingly, the costs for patients involved in this clinical trial with the initial instruction and the follow-up was about $6,000 per patient. In the group setting in the YMCA, the cost was cut down to about $400.

In terms of scaling this, for example, if we could expand this, we have not done any economic analysis on this, but there is a private group called the Urban Institute that has recently looked at what happens if you could scale this. They estimate, given those numbers, about $191 billion could be saved over a 10-year period, with some very conservative assessments or assumptions, if this could go to scale.

CANCER RESEARCH

Senator MURRAY. Well, that is impressive.

Dr. Lowy, let me ask you, as Dr. Collins mentioned, we have seen some significant progress in recent years in the use of immunotherapy to treat certain forms of melanoma lymphoma and lung cancer. I believe there is universal support on the subcommittee for efforts to find similar breakthroughs for other cancers. I want to ask you, what is NCI doing to make that happen? And where is the potential for new cures the greatest?

Dr. LOWY. We are investing in a number of different areas throughout the cancer spectrum. I think that there are opportunities in many different areas.

For example, we are investing heavily in pancreatic cancer, because this is a cancer where we have not had significant progress despite long-term recognition of how serious this cancer is.

We also are investing research in pediatric interventions, and recently NCI supported researchers have develop two new interventions against pediatric leukemia and lymphoma. And this was initially developed in the academic sector and has been picked up by venture capital, and is rapidly going forward for clinical trials.

We also are interacting with the pharmaceutical industry to try to identify new and important uses for drugs that are off-the-shelf, either because they have been approved for one intervention but not for another. For example, BRAF inhibitors in melanoma, trying them in other diseases. This is potentially a very important innovation, because we recognize that a percentage of patients who have different kinds of cancers may actually have the same molecular abnormalities and, therefore, may benefit from targeted treatments initially developed in other areas.

I could go on but I think that given the time——

Senator MURRAY. Could you just tell me why immunotherapy is effective in some patients but not in others who have the same cancer?

Dr. LOWY. Yes. I think that this is a critically important issue. I think what we are doing to support research to understand mechanisms is critically important because if we could understand why some patients are benefiting, whereas others are not, that increased understanding should lead to better interventions for the people who currently are not responding. Or at the very least, we would not be giving them treatment for which they are not going to benefit.

Senator MURRAY. So it is a question we need to answer with more research.

Dr. LOWY. Yes.

Senator MURRAY. Okay, thank you very much.

Senator BLUNT. I will go last in this second round, so, Senator Shelby.

REPLICATION OF RESEARCH

Senator SHELBY. I will be as fast as I can. Thank you, Mr. Chairman.

Dr. Collins, there have been several articles regarding biomedical study results, including those funded by NIH, that appear in top peer-reviewed journals that cannot be replicated or reproduced. One of the articles cited a Bayer study describing how it had halted 64 percent of its early drug target projects because in-house experiments failed to match claims made in the publication.

You have done a study on this. What is the problem here? Why can't they replicate? Is it rushing to print too fast? What is it? Would you discuss that?

Dr. COLLINS. Senator, it was you who first brought this issue to attention in a hearing about 3 years ago as it was just beginning

to appear. I appreciate very much your having shined a light on a situation that we are taking with great seriousness.

This is a complicated, multi-factored situation. I am actually showing up on the screen what NIH has now posted as far as a summary of all the things we are engaged in to try to address this, and also to do things to improve the training of the next generation of scientists about these issues, in terms of rigor and reproducibility.

I would say, of the factors that are involved, certainly the hypercompetitive atmosphere that currently exists, much of it on the basis of the fact that funding is so tight, causes people to try to get publications out as quickly as possible. That may, in fact, result in circumstances where the replication study didn't quite get done. And therefore, somebody else finds out later it would not have worked.

We have an issue in terms of journals also, in many instances, not having been as thorough as they should in evaluating manuscripts.

I am happy to say that through the leadership of Dr. Lawrence Tabak, the principal deputy, we convened the journals to talk about this. Now more than 150 journals have signed off on a checklist that they use when papers come in to be sure that the experimental details are there, the statistical methods are described, and so on.

It clearly is something, though, that touches many areas of science. Dr. Lorsch has been leading an effort where we are looking at projects on cell lines, because sometimes people publish a paper about work on a cell line and it turns out that cell line was not what they thought it was. These things get passed around.

Training is critical. We actually have some training videos up on the site, if you want to see what we are now asking mentors to use in lab meetings and other group meetings, to try to bring to the attention of trainees these critical issues about study design, how you set up an experiment where you know that you have done it rigorously.

So we are all over this, and we are, in fact, pushing pretty hard to see this problem addressed.

It will always be the case that science gives you results that, later on, you cannot seem to make sense out of. But if that happens, we want it to happen in a way that was unavoidable, not because people were actually cutting corners.

I think we have the whole attention of the community now to this, and you are going to see the problem get less than it had been. I hope much less.

Senator SHELBY. But this is a very important question, because it goes right to the essence of the investigation and replicating what you have found or discovered and what we benefit from. Is that correct?

Doctor, do you want to comment on that?

Dr. KOROSHETZ. Yes, I was going to add one other point. We have looked at this at our Institute, and there is another side to this, which is that for some of these things, it is not that you can't reproduce them. It is that given the effort that you put in, you didn't reproduce them.

So we have, for instance, really interesting technologies. When you first try to reproduce it, you can't do it. But when the people who develop the technologies open up their labs, people can go in and learn how to do it, and then it works.

Senator SHELBY. So some of them were on the right road, but they just did not have the means to finish it?

Dr. KOROSHETZ. That's right.

Senator SHELBY. Thank you, Mr. Chairman.

Senator BLUNT. Thank you, Senator.

Let's go to Senator Cassidy and then Senator Moran.

BASIC SCIENCE OF ADDICTION

Senator CASSIDY. First, I misspoke last time. $66 million is not 21 percent of the NHLBI. That was too much. But nonetheless, the point is taken. The best we can find out, it is about 1,800 people who die of HIV with cardiovascular disease. We are spending $66 million on it.

Dr. Volkow, I heard people say that the basic science of addiction and mental health is a barren field. I am not a mental health professional nor an addictionologist. But I am just asking, do you feel as if you had, to take the question asked earlier, significant more resources, would you be able to do the clinical and basic science to make significant advances in the area of addictionology? And could you speak to that for mental health as well?

Dr. VOLKOW. Yes. Definitely, we could accelerate a lot of the discoveries. And I apologize, Senator, but I am going to disagree, because I would not say the research on mental health and substance abuse disorders has been barren as it relates to over the past 10 years, 15 years, a really expanded understanding about the abnormalities in the brain of people who suffer from mental illness.

Senator CASSIDY. I accept that. Actually, I did not know enough to disagree, but you would say there is great academic progress?

Dr. VOLKOW. There has been great academic progress, and that has enabled us to identify potential targets for treatment.

But there is a problem going——

Senator CASSIDY. Can I stop you?

Dr. VOLKOW. Yes.

FUNDING NEURODEGENERATIVE RESEARCH

Senator CASSIDY. Dr. Koroshetz, again, the issue on Alzheimer's dementia and ALS and Parkinson's, I heard people say the promise is not there as it might be in other fields.

I also have parents with dementia and Alzheimer's. I want to give you a lot of money. I am hoping to convince my colleagues who have more sway—that is where they go ahead of me, they have more sway than me—to do so as well. Would that be a worthy investment? Is there academic promise in those fields, that if you got the money, you can do the basic research, clinical research, et cetera?

Dr. KOROSHETZ. I think the neurodegeneration field, in general, is bringing in lots of really smart people to try to solve these problems. So we have the workforce. I think with the resources, we could really make hay.

As I said before, there are a couple things that are really tantalizing now, and that is that all the neurodegenerative diseases—Parkinson's, Alzheimer's, ALS—all have one common feature. The cells that die have proteins that aggregate and get stuck in those cells.

So, people really are on the idea that maybe there is a unified theory. If we can stop this process for one disease, we can stop it for all of them.

So, it is a leap of faith right now, but there is evidence that this is not impossible, that we can make a big breakthrough.

Senator CASSIDY. Dr. Collins.

Dr. COLLINS. I would just like to add to that——

Senator CASSIDY. I have a question for you, Dr. Collins.

Dr. COLLINS. Okay, this will be quick. Just basically, the point here is that you are never quite sure where the breakthroughs are going to come from. We have to be careful not to overly target research plans in a direction of a specific disease because the answer might come out of some very different investigation or some very basic science, as we are celebrating today with the Nobel Prizes.

Just a quick example, the biggest breakthrough that I have heard about in the last month for ALS——

DECISION MAKING

Senator CASSIDY. No, can I just stop you? I have a minute and 45 seconds. Can I stop you for a second?

You have a bunch of bright, aggressive people who they would not be who they are were it not for you being the pinnacle. Believe me, I am a doc. I know you are the pinnacle of the docs.

You mentioned earlier the academic promise, the research promise, of HIV/AIDS as a rationale to somewhat continue there. I guess what I was trying to figure out is, is it lacking elsewhere? One of the excuses—or one of the reasons, I should say, to continue the funding in one area as opposed to others is the apparent academic promise in the one as opposed to the others.

How do you balance each of these folks who have such promise in their field as you make that decision?

Dr. COLLINS. That is a great question. That is something we talk about every day around the table.

Certainly, in every one of these Institutes, there are areas that are up-and-coming and others that perhaps are not quite as rapidly moving. We are constantly trying to adjust the decisionmaking, but also not trying to be overly top-down in making decisions because a lot of the great ideas come from our wonderful scientific community out there, and we cannot always anticipate where they are going. So it is a constant revision day by day, week by week, of where we want to put the emphasis.

Senator CASSIDY. Okay.

And if my wish were fulfilled and dollars were redirected from HIV/AIDS into some of these other areas, it sounds like there are fertile fields that that money would, indeed, fertilize and hopefully sow great benefits.

Dr. COLLINS. There are fertile fields all across our landscape.

Senator CASSIDY. Okay, I yield back. Thank you.

Senator BLUNT. Senator Moran.

ALS

Senator MORAN. Mr. Chairman, thank you.

Dr. Collins, the most significant development that has occurred in the last 30 days is? On ALS?

Dr. COLLINS. Okay, thank you. It sort of fits with the conversation we are having.

It was an investigator who is actually studying HIV/AIDS and trying to understand one of the comorbidities, which is a neurological problem, which resembles ALS in a modest way. This is an intramural investigator, Avi Nath.

He discovered that there is an activation of an endogenous retrovirus that we all carry around called HERV and that it starts making copies of itself and it causes this damage to the neurological system, particularly those anterior horn cells. This looks very much like ALS. And in fact, the publication, which just came out, suggested that this might be one of those missing clues to what is happening in Lou Gehrig's disease, not for people who have HIV at all, but who have similar symptoms.

I don't know where that is going to go. Dr. Koroshetz probably could tell you a lot more about the details.

But it was an interesting example where you are studying this disease over here, and you learn something about that one over there, and you didn't expect that to happen.

Senator MORAN. Thank you.

UPDATE ON PEDIATRIC MATCH TRIAL

Dr. Lowy, welcome to this panel. I look forward to getting better acquainted with you. I just want to give you the opportunity to express, as the relatively new Acting Director, your vision for the National Cancer Institute. I particularly wanted to highlight a program that is being launched, a pediatric clinical trial called Pediatric MATCH trial, and can you tell me about that and where you see it going and what it may mean.

Dr. LOWY. The Pediatric MATCH trial, Senator, is a trial that is currently under development. What it does is essentially do for pediatric cancer research what the Adult MATCH trial that started 2 months ago is doing for adults who have advanced cancer for which there is no standard treatment.

It puts the molecular abnormality of the patient front and center, rather than the origin in the body of where it occurs. And it takes drugs that are off-the-shelf, either experimental drugs or that have been approved for other uses, and it tests them in these other ways for cancers where they are not yet approved.

The goal is to improve the outlook for these patients. This is a trial that, as I said, is under development and one of the uses for the Precision Medicine Initiative, the oncology portion, that people have been talking about.

Senator MORAN. And your vision for NCI?

Dr. LOWY. The overall vision for NCI is to support basic research, as we have done historically, to invest in precision medicine, not just in the areas of cancer treatment, as is occurring with the Precision Medicine Initiative and the oncology portion, but also to emphasize precision medicine in the area of cancer prevention and

cancer screening, understanding better the causes of cancer, understanding better how cancer comes about, and, in addition, to put a focus on health disparities in cancer.

Unfortunately, there are many different kinds of cancer where certain underrepresented minorities have a much higher incidence of mortality, and we need to treat these populations as we would any high-risk population to understand the biology, the lifestyle factors, and the utilization of medical utility, and, in addition, to try to mitigate these factors just as we do for any high-risk population.

These are some of the important areas that we are looking forward to making progress in.

Senator MORAN. Thank you very much. I wish you well.

Mr. Chairman, thank you for this hearing. Thanks to you and Senator Murray for your leadership in this area of medical research.

SUPPORT FOR INNOVATIVE RESEARCH

Senator BLUNT. Well, thank you, Senator Moran.

Dr. Lorsch, when Senator Moran was the ranking member on this Committee, they started an effort like the Defense Advanced Research Projects on high-risk. I think it was fiscal year 2014.

You mentioned high risk, high reward, a couple times. Give a couple examples of either things that did work out, or things that did not that we should be thinking about when we think about going to a high-risk area as opposed to something that is more likely to produce a result, but maybe not nearly as big of a result.

Dr. LORSCH. I think the recent developments in gene editing are an example of something that was an out-of-the-box idea. Could you use this bacterial system that allows rearrangements of genes and then use it to edit genes in a mammalian cell to possibly repair those genes in a diseased state? That is something, as you may know, that has recently worked and has taken off and is revolutionizing biotechnology and has the promise to revolutionize medicine in a variety of ways. I think that is a great example of that.

Dr. COLLINS. I might mention that the Common Fund at NIH, which the Congress made into a permanent part of our budget back in 2006, is a place that specifically aims to try to support these high-risk, high-reward projects that no single Institute would probably be able to invest in, but collectively we can.

A couple examples there. The microbe biome, this effort to understand how the microbes that live on us and in us that actually outnumber us if you start counting up cells, how do those play a role in our health and in the cause of disease.

This has been an absolutely revolutionary set of insights coming about because of new technologies that allow us to find out what is there and how it changes over time. That was one of those high-risk, high-reward programs that has now changed the whole landscape of how all the institutes are doing research because you really do not want to think of the human as an organism now. You want to think of us as superorganisms. It is both us and the microbes, and it is the interaction between the two that makes a big difference. That is an example.

Another one, which is closer to clinical medicine, is to try to come up with a really standardized, reliable way of patients reporting outcomes from their perspective. So much of clinical research is the researchers or doctors saying here is what we think happened to this patient who was given this treatment. You want to hear what the patient thought, too. Sometimes it is not quite the same thing.

But we have not had those majors, so a program called Promise, which many people thought this was going to be really hard, has actually transformed that process. It makes it possible now for us to run more clinical trials where the patients are not really patients. They are partners. They are full participants. Their input is guiding our decisionmaking about what works and what doesn't.

Senator BLUNT. I think Washington University is doing some of the microbial work.

Dr. COLLINS. They are. Jeff Gordon, your heroic figure there at Wash. University is one of the main leaders in the world.

Senator BLUNT. And unlike the genetic structure, the microbial structure is changing all the time and how you impact that is the question here. Is that right?

Dr. COLLINS. That is right. And as we are now mounting this Precision Medicine Initiative, thinking about following 1 million Americans over time, to know what is happening to their microbe biome would be enormously interesting, as a consequence of diet, exercise, the presence of illness or not, taking antibiotics. We could find this out on a scale not previously imaginable once we get this up and going.

Senator BLUNT. Right.

OPIOID AND HERION ABUSE

I am going to come to you, Dr. Volkow. Senator Murray mentioned earlier the cut to the block grant fund. In fact, we cut lots of programs in this budget to begin to reorient the bill towards other priorities. In fact, I think we eliminated totally funding for 43 programs that this year we are spending $1.25 billion, all of which had very good titles. There was not a single title that was not meritorious.

But the process of prioritizing is exactly that. You do not really prioritize if all you do is get more money and spend it on something more important than you thought you were spending on last year. That is not really prioritizing. That is just adding more money on top for good things.

But what brought me to that when I thought about, well, we did cut those block grants by about 3 percent. But the majority of that money, in my view, went into increasing the money to combat opioid abuse, which, frankly, a handful of years ago I hadn't heard of at all. But in Committee hearings this year, we heard about it all the time.

Would you talk a little bit about both opioid abuse and what research may be going on to come up with pain medicines that are less easily abused, and less easily converted to other drugs to be used in other ways? That would be helpful.

Dr. VOLKOW. Yes, indeed. Unfortunately, you are hearing about opioids because of their devastating consequences. So on the one hand, we have basically seen 16,000 people die from prescription

opioid overdoses. Over the past 6 years, we have seen a fourfold increase in people dying from heroin. So it was stable for many years, at around 2,000 deaths per year. And in the past 5 years, it has increased to over 8,000 deaths in 2013. So we are seeing a really steep increase in deaths from prescription opioids and now from heroin.

That has led us to realize the nature of the problem. So on the one hand, we have the reality that there are many patients suffering from chronic pain but we do not have sufficient alternatives, as I was mentioning before.

So in partnership with the pain consortia at NIH, NIDA is trying to develop alternative medications that are effective for severe pain that are not addictive. We are trying to also partner with the pharmaceutical industry to develop opioid medications that will not be diverted.

We are partnering, of course, with the funding agencies. And the FDA recently approved some new indication that an opioid medication cannot be diverted.

We are also encouraging the better education of the healthcare providers on how to screen properly for pain and how to manage opioids, and how to, of course, screen for substance use disorders.

So there is a multipronged approach, both from the perspective of NIH with various Institutes working together and at the same time with our sister agencies.

Senator BLUNT. And I would think one of those groups may be whatever is happening in the Defense Department research on this topic because, certainly, servicemembers and veterans have a really high propensity to find themselves in that trap of becoming addicted to the pain medicines that they are given, often because of their service-related injuries, and that cannot be a good thing.

Dr. VOLKOW. You are pointing at something that, unfortunately, not many people are aware of. The prevalence of pain in military people returning is much higher. As a result of that, they are much more likely to be given prescription opioids, much higher than the rest of the public.

Therefore, the number of people who are dying from prescription opioids among the military is higher, just by the fact of what you are saying. They are suffering from pain, and we do not have many pain alternatives, so they receive opioid medications.

Senator BLUNT. Well, thank you for your help on that.

Senator Shaheen.

Senator SHAHEEN. Thank you, Mr. Chairman.

I would like to follow up on the concerns that you are raising about opioid abuse and also heroin, the fact that it has led to a heroin epidemic. That is a huge challenge that we are facing in the Northeast and across this country.

I can tell you that in my little town of Dover with a population of about 20,000 people, they had two recent deaths just in 1 day from drug overdoses. I think it should rise to the level of the kind of cross-agency—it is a crisis, and I appreciate that you all have a different mission in terms of research. But this is something that the medical community, the law enforcement community, the treatment community, all need to be working on together. Until that

happens, we are going to continue to see this crisis escalate. It is already out of control, and it is only going to get worse.

So when, in a small town in New Hampshire, you can buy a bag of heroin for less than you can get your prescription filled for $7 a bag, then we have a real problem.

So I want to make that point, because I am not sure if there are other ways in which you all are looking at addressing this issue, beyond just the challenge of opioids. And the extent to which that gets people addicted, are there other things you are looking at with respect to the opioid and heroin epidemic that is going on in the country right now? I am happy to direct that to whoever would like to take it.

Dr. VOLKOW. Yes, indeed. Again, it is a devastating situation, but one of the reinforcing things to me has been how integrated the agencies have been in working together to come up with solutions and how these solutions are actually coming into very specific action items, like the FDA approving new indication for deterrent formulations, like the DEA coming up with let's bring back all those opioid medications that are not being used.

These actually are resulting in effective interventions. So there is a very strong, concerted effort.

The good news is that there are medications that we currently have that are effective for the treatment of people that become addicted to those opioid prescriptions. The challenge is that they are not being implemented. So we are working with agencies to actually develop implementation strategies to increase it, to provide medications for the patients that would be easier to take so that they are compliant.

USE OF NARCAN

Senator SHAHEEN. Right. Sorry to interrupt.

So does NIH have a view on whether Narcan should be available over-the-counter to families, not to law enforcement or other people who actually do interventions, but to families who are concerned about drug overdoses and their families? Is that something that you think should be readily available?

Dr. VOLKOW. I think we are extremely lucky to have Narcan. We should make it as widely available as possible.

Senator SHAHEEN. Thank you.

I would just urge NIH to think about all of the ways in which you can engage on this issue, because it is, as you know, out of control and getting worse, not better, despite all of the coordinated efforts. We see those in New Hampshire and other States that are dealing with this issue, but we still have not made it, I think, the kind of all-hands-on-deck priority that it should be.

Dr. COLLINS. I would just add to that, there is a lot of interagency work on this. There is interagency pain research coordinating committee that meets. It is all the Federal agencies. I think they are doing very good work. We have education programs.

COORDINATION OF EFFORTS—STATE AND FEDERAL

Senator SHAHEEN. Can I just interrupt? So how are they coordinating the work that they are doing at the State level, with States that are dealing with this issue?

Dr. COLLINS. I would have to get back to you on the State level, because that is something that we have not really approached. But there is a national pain strategy that we are working on through HHS to be cleared soon that addresses some of these problems.

There are education programs that NIH funds. One of the issues is really educating the practitioners on the actual proper use. So we have centers of excellence for education on how to manage pain that NIH funds. HHS has a tremendous video for education of practitioners on the use of narcotics and best management of pain, trying to reverse this problem.

Senator SHAHEEN. Well, I do not know how we make sure that States are aware of the work that is going on, but, certainly, that seems to be one of the coordinating points that has to happen in order to better address the crisis. So I would urge that you all think about that, and if we can be helpful in thinking about how to make sure that that kind of information and effort is available.

Dr. COLLINS. I would just add quickly, Congressman Hal Rogers, who has been such an effective leader in terms of bringing attention to this, runs a summit every April and brings in the States. And Dr. Volkow and I have been at that summit each time for the last couple years. Tom Frieden, head of the CDC, comes.

It is an opportunity for States to really hear what the opportunities are that are being thought about across the Nation. It is probably not enough because, as you say, we are still in the thick of a very serious epidemic. But those connections are trying to be made, and I have to give Congressman Rogers a lot of credit for being a convener.

Senator SHAHEEN. Thank you.

Senator BLUNT. Thank you, Senator Shaheen.

Dr. Collins, thank you and thank you for the fine representation of your team. As you suggested, there are even more on the bench that you could call in at some future time for a hearing. We might ask you to do that.

ADDITIONAL COMMITTEE QUESTIONS

Over the next week, the record will stay open for questions. I know Senator Alexander and others have already put some questions out there, and I am sure you will get some.

[The following questions were not asked at the hearing, but were submitted to the Department for response subsequent to the hearing:]

QUESTIONS SUBMITTED TO DR. FRANCIS S. COLLINS

QUESTIONS SUBMITTED BY SENATOR ROY BLUNT

ALZHEIMER'S FUNDING

Question. Dr. Collins, the Senate received the NIH's first bypass budget for funding Alzheimer's disease which requested an increase of $323 million for fiscal year 2017.

—Given that the Senate Labor/HHS bill for fiscal year 2016 provides more funding ($350 million) than what NIH requested for fiscal year 2017, how would the bypass budget be changed for next year?

—Can we assume all of the requested research projects for fiscal year 2017 would, instead, be done in fiscal year 2016 if the Senate funding level for NIH is enacted?

—Dr. Collins, how do you prioritize funding for a disease when you know, as in the case of Alzheimer's disease, that the disease burden is only going to increase over the next 20 years?

Dr. Collins, has Alzheimer's research had significant application to other major disease research efforts? What crossover benefits have we seen from increasing Alzheimer's research funding?

Answer. NIH recognized that a substantial increase in funding for Alzheimer's disease (AD) for fiscal year 2016 would have an impact on the implementation of the milestones linked to the fiscal year 2017 Bypass Budget. To address this possibility, NIH created a separate plan for accelerating many of the activities outlined in the fiscal year 2017 Bypass Budget milestones to be initiated in fiscal year 2016. Under this circumstance, the fiscal year 2018 Bypass Budget would reflect this acceleration and include estimates for targeting new goals from its overarching list of long-range milestones.[1]

Not all of the projects outlined in the fiscal year 2017 milestones can be accelerated into fiscal year 2016, even if the Senate funding level for NIH is enacted. For example, the creation of new cohorts to accelerate the identification of gene variants and other risk and protective factors is a lengthy, detailed, and labor-intensive process, as it involves the collection of large amounts of data, including informed consent from thousands of participants. In addition, some research areas require further development and will be explored further in fiscal year 2017. These include aging processes in human cell models of AD; the planned biorepository for AD biological samples; translational bioinformatics; and validation of the NIH Toolbox for Assessment of Neurological and Behavioral Function, among others.

NIH recognizes that the public health burden of AD will only become larger, if preventative therapies and treatments are not established. AD is a prominent focus of the Accelerating Medicines Partnership, a major public-private partnership between NIH, FDA, 10 biopharmaceutical companies and multiple non-profit organizations to transform the current model for developing new diagnostics and treatments by jointly identifying and validating promising biological targets for therapeutics.

Increased support for Alzheimer's has advanced our knowledge not only of that disease, but of other diseases and conditions, as well—most notably other neurodegenerative diseases such as frontotemporal dementia (FTD). For example:

—The efforts toward discovery and standardization of imaging biomarkers made in Alzheimer's are being leveraged in other neurodegenerative diseases, such as FTD and Parkinson's disease.

—Investments in fluid biomarker discovery using various "omics" technologies—metabolomics in particular—are geared toward the identification of biomarkers that can be used to stratify patients for clinical trials, and identify participants most likely to respond to a specific therapy, for both AD and related dementias.

—NIA has funded research on the development of human induced pluripotent stem (iPS) cells for AD modeling. Further studies have shown that such use of "disease-in-a-dish" models can be effectively used to study molecular mechanisms underlying not only AD, but also other neurodegenerative and neurodevelopmental diseases.

Systems biology approaches aimed at identifying complex genetic and molecular networks, such as the Accelerating Medicines Partnership (AMP), will enable the identification of molecular signatures and networks underlying the various disease processes that lead to symptoms associated with AD. These efforts will lay the foundation for precision medicine for AD and other dementias (i.e., it will enable us to treat the right disease process with the right drug at the right time). The AMP–AD systems biology efforts will also enable us to identify molecular events that are shared between AD and other disorders. This could facilitate successful repurposing of drugs that prove effective for AD for their use in other neurodegenerative conditions with similar underlying pathologies—and vice versa.

Finally, NIH-supported Alzheimer's genetics initiatives have provided genetic information relevant to several unrelated conditions, including autism, congenital heart disease, scoliosis, pain, cancer, and neurologic disease. In 2012, the NIA Genetics of Alzheimer's Disease Data Storage Site (NIAGADS) and the Database for Genotypes and Phenotypes (dbGaP) formed a unique partnership in order to efficiently provide data to the research community. Through this exceptional arrangement, dbGaP's capacity to work with specific genetics user communities was augmented. The interface between the two databases now serves as a prototype for other genetics user communities; similar designs are being explored or planned by three other NIH Institutes (NINDS, NHGRI, and NHLBI). Most recently, the

[1] Https://www.nia.nih.gov/budget-files/alzheimers-disease-research-implementation-milestones-2013-2025.pdf.

Gabrielle Miller Kids Fund Common Fund initiative has engaged NIAGADS for discussion on design of a similar interface.

PRECISION MEDICINE

Question. Dr. Collins, at our hearing in April, we discussed the revolutionary idea of Precision Medicine. Since that time, NIH has made progress on developing a plan to move this initiative forward and stakeholders have been able to express their thoughts about the plan. I have heard several concerns from cancer researchers about the 1 million person cohort. In particular, researchers have expressed concern about what scientific question a cohort would be answering and how the NIH would ensure the cohort includes a proportionate representation of Americans, particularly individuals from racial and ethnic minorities.

What are your views on these concerns and can you discuss how the cohort would be setup to take into consideration these concerns and how a 1 million person cohort will inform the initiative?

Answer. The appropriate size, composition, and research power of the Precision Medicine Initiative® (PMI) cohort were major foci of the deliberations of the PMI Working Group of the Advisory Committee to the Director, which delivered its blue print for the PMI Cohort Program on September 17, 2015. The Working Group included renowned experts from all sectors: private and public sectors, academic research, clinicians, and participants. Their deliberations and recommendations were informed by four major national workshops, two requests for information, and a public survey. The primary objective of the PMI Cohort Program will be to enroll one million or more volunteers into a cohort that broadly reflects the diversity of the U.S. population, and to follow their health and clinical outcomes over time. The PMI Working Group report has been widely embraced and applauded by the scientific community including industry and patient groups.

NIH has now released a number of funding opportunities to solicit the very best ideas from the scientific community to build the PMI Cohort (https://www.nih.gov/precision-medicine-initiative-cohort-program/funding-opportunities). The funding opportunities specifically request that applicants address past experience with inclusion of diverse populations and provide specifics plans a capabilities for doing so as a part of the PMI Cohort Program. The potential of this diverse cohort of one million or more presents a spectacular variety of scientific opportunities, including:

—Develop quantitative estimates of risk for a range of diseases by integrating environmental exposures, genetic factors and gene-environment interactions
—Identify the causes of individual variation in response to commonly used therapeutics (pharmacogenomics)
—Discover biological markers that signal increased or decreased risk of developing common diseases
—Use mobile health (mHealth) technologies to correlate activity, physiological measures and environmental exposures with health outcomes
—Develop new disease classifications and relationships
—Empower study participants with data and information to improve their own health
—Create a platform to enable trials of targeted therapies

PMI AND NATIONAL CHILDREN'S STUDY

Question. Congress appropriated over $1 billion over a decade for a cohort of children as part of the National Children's Study (NCS). The NCS was plagued with problems, in particular with composing a cohort that adequately reflected the diversity of Americans. It eventually was ended in 2014 with virtually no studies being conducted and $1 billion being spent. How do we ensure that this will not happen with the Precision Medicine cohort?

Answer. In order to pre-emptively identify and address challenges that the Precision Medicine Initiative (PMI) Cohort, a large-scale, longitudinal cohort, might face, the PMI Working Group consulted on this issue with research cohort management experts including David Murray, the NIH Associate Director for Prevention who is tasked with managing the closure of the NCS, and Sir Rory Collins, the Chief Executive of the UK Biobank and a member of the PMI Working Group. These consultations resulted in a number of "lessons learned" for both successful (the UK Biobank was able to bounce back after initial challenges) and unsuccessful (NCS was unable to find its footing) large-scale cohort studies. These lessons included the suggestion to guide the cohort design with a limited set of research questions; to require partners to provide high degrees of data standardization and centralize core data; to select a sampling approach that is efficient and feasible; to design a strong and nimble governance structure that is aware of and rapidly responsive to changes in the so-

cial, technological, and scientific elements arising in a cohort over time; to carefully select the right funding mechanisms for the project scope; to carefully test new procedures in small pilots; and to ensure that enrollment is convenient.

These "lessons learned" were incorporated into the PMI Working Group recommendations for the PMI Cohort Program. For example, the Working Group began its work by defining the scientific questions it expected the cohort to be able to answer. It recommended a core data set required for partner organizations and volunteers that will be collected in a centralized data center, with federated inquiries available for other data. It recommended an approach that favors diversity over representativeness, and a small and powerful governance structure, composed primarily of one director and a small executive committee, that will ensure that the PMI Cohort Program can be immediately responsive to necessary changes in the program's structure. The NIH carefully examined the best funding mechanisms for each element of the program, and proposes early pilots that will allow us to carefully test and retest the program elements, including proposals to test the best way to enroll participants directly as well as through healthcare provider organizations (see Blunt Question: PMI Accuracy and Quality).

PMI ACCURACY AND QUALITY OF DATA

Question. Dr. Collins, it is challenging to deal with the accuracy and quality of data when it comes from multiple sources. How will the Precision Medicine cohort deal with this issue?

Answer. The accuracy and quality of the Precision Medicine Initiative® (PMI) cohort data was another focal point of discussions for the PMI Working Group of the Advisory Committee to the Director. The PMI Working Group included multiple experts in the field of bioinformatics and "big data" research, all of whom emphasized that data standards should be developed before data collection begins, given that the use of data standards promotes quality science, consistency in data use and reuse, and meta-analysis. PMI Working Group deliberations and recommendations were also informed by four major national workshops, one of which focused specifically on scientific and methodologic considerations to maximize the quality, accuracy, and utility of detailed health information for PMI Cohort participants. The PMI Working Group made a number of recommendations that NIH will implement in order to ensure accuracy and quality of PMI data coming from multiple sources, such as recommendation to create a data coordinating center that will be responsible for the storage, management, and transmission of a curated and analysis-ready core set of data; to develop a system whereby the details of data collection and curation will be agreed upon between data collection sites and the data coordinating center before data collection begins; to adopt and utilize existing data standards to the greatest extent possible and require the use of common data models to develop a structured core data set that can be distributed to researchers; and to establish a data subcommittee of the PMI Cohort Program governance structure to oversee ongoing data collection and ensure that the program maintains high quality, accuracy, and utility.

QUESTIONS SUBMITTED BY SENATOR JERRY MORAN

ALZHEIMER'S DISEASE RESEARCH

Question. Following the Alzheimer's Disease Research Summit last February, NIH is poised to revise the research milestones created by the National Plan. When can we expect to see in the updated milestones? To what extent do those milestones match the recommendations that were printed in the journal Alzheimer's & Dementia in October of last year? Does NIH intend to release program announcements that are tied to the milestones document?

Answer. NIH released two related sets of research milestones, along with the fiscal year 2017 Alzheimer's Disease and Related Dementias Bypass Budget, on July 27, 2015. One was a broad set of Alzheimer's-specific milestones that included a number of long-range research goals that extend to 2025: https://www.nia.nih.gov/budget-files/alzheimers-disease-research-implementation-milestones-2013-2025.pdf. These milestones reflected recommendations made across the diverse range of research topics covered at the 2015 Alzheimer's Disease Research Summit. NIH also released a set of fiscal year 2017-specific milestones for Alzheimer's and related dementias (https://www.nia.nih.gov/budget-files/fy-2017-alzheimers-disease-bypass-budget-milestones.pdf). The latter milestones were used to develop the fiscal year 2017 Alzheimer's Disease and Related Dementias Bypass Budget: https://www.nia.nih.gov/budget-files/Reaching-for-a-Cure-Alzheimers-Disease-and-Related-

Dementias-Research-at-NIH.pdf. Thirteen NIH ICs contributed to the fiscal year 2017 milestones, and they were informed by two scientific meetings (in addition to the 2012 and 2015 Alzheimer's Disease Research Summits), the 2013 conference on Alzheimer's Disease-Related Dementias, and the 2013 meeting on Advancing Treatment for Alzheimer's Disease in Individuals with Down Syndrome.

With respect to the relationship between the NIH's established milestones and the recommendations for updating the 2012 milestones published in the journal Alzheimer's & Dementia, there is considerable overlap. The recommendations published in the academic journal reflect input assembled by a non-Federal funding organization, and NIH took these recommendations into consideration as it produced its latest published research milestones.

Ten Funding Opportunity Announcements (FOAs) were released by the NIA in the fall of 2015 to address the updated research milestones and offer flexibility for funding in a wide range of budgetary circumstances. The FOAs have set-aside funds associated with them, and will be supported according to the availability of funds in fiscal year 2016 and fiscal year 2017. They fall into seven broad categories, and offer opportunities for investigators in virtually every aspect of AD research—including health disparities, caregiving, epidemiology, diagnosis and prediction, molecular and cellular mechanisms, brain aging, and clinical trials. These FOAs incorporate themes and recommendations from the 2012 and 2015 Alzheimer's Disease Research Summits. The categories are intentionally wide-ranging and each FOA is important in its own way.

BRAIN INITIATIVE

Question. What would be the biggest impact of a shortfall in the projected funding for the BRAIN Initiative?

Answer. The biggest impact lies in the inability to fully, and in a timely manner, realize the bold, ambitious goal of the BRAIN Initiative: to revolutionize our understanding of the human brain, and empower researchers seeking new ways to treat, cure, and even prevent brain disorders.

The gap between NIH's fiscal year 2015 budget request for the BRAIN Initiative, and the funds actually appropriated, has two direct consequences. First, it delays the overall pace at which NIH can scale-up its efforts for the BRAIN Initiative, causing scientific progress to fall further and further behind the 12-year plan laid out by the Advisory Committee to the NIH Director (ACD) in their report BRAIN 2025: A Scientific Vision. The BRAIN 2025 plan outlines a step-wise sequence of research with subsequent steps dependent upon prior success. Shortfalls in funding slow the stepwise progress. Secondly, it forces NIH to scale back the scope of research being funded under current Funding Opportunities which leads to gaps that could undermine the solid foundation laid out in the BRAIN 2025 plan. As one example, a major project in the BRAIN Initiative is to assemble research teams to collect, analyze, and share data from recordings of the human brain. This project was vetted by the external scientific experts that compose the BRAIN Multi-Council Working Group and was announced to the scientific community in fiscal year 2015. However, the grant solicitation process was halted due to the gap between the budget request and appropriated funds. This project and the fiscal year 2016 projects described below are ready to launch pending budget availability. In general, the competition for the fiscal year 2015 BRAIN Initiative awards was extremely competitive and funds were insufficient to support many otherwise excellent proposals.

The BRAIN Initiative is focused on developing neurotechnologies that enable scientists to understand the functions of specific brain circuits, including circuits relevant to neurological disorders such as Parkinson's disease, epilepsy, recovery from traumatic brain injury and stroke, mental illness, and addiction. To achieve this goal, NIH is funding teams of engineers, physicists, chemists, and neuroscientists to develop devices that can record and modulate activity in the brain at scales that span from single neurons to entire brain regions. This work promises to enable accurate early diagnosis of disorders of brain circuit activity such as depression, autism, and schizophrenia, as well as to build upon the success of deep brain stimulation for Parkinson's disease to develop new ways to reduce suffering caused by a variety of neurological and mental illnesses. Funding shortfalls inevitably lead to delays in achieving such goals. These delays mean that people suffering now with devastating brain diseases and disorders may have to wait longer for the treatment breakthroughs that could transform their lives and the lives of their families and communities.

ALZHEIMER'S DISEASE RESEARCH

Question. Recent budgets have included money to expand research efforts related to Alzheimer's disease. Can you tell me about some of those efforts and things you hope to achieve in the next few years?

Answer. New investments include large-scale research for identification of new risk and protective genes; development of new cellular models of the disease to enable rapid screens of potential therapeutic agents; establishment of translational centers that will support drug discovery and development; and groundbreaking prevention trials in people at the highest risk of disease. Joint initiatives are identifying imaging and fluid biomarkers that enable us to detect and track the onset and progression of Alzheimer's-related brain changes. Clinical trials are now underway testing therapies in pre-symptomatic volunteers at risk for developing Alzheimer's. These ground-breaking trials may lead to the long-sought interventions that can directly influence the underlying pathology. Collaborations among NIH, the biomedical industry and advocacy groups—such as the Accelerating Medicines Partnership—are overcoming traditional barriers to drug discovery.

Other new investments include the Alzheimer's Disease Sequencing Project supporting the analysis of whole exome and genome sequencing data; testing of anti-amyloid drug interventions through the Alzheimer's Prevention Initiative APOE4 trial and the Dominantly Inherited Alzheimer's Network Trials Unit (DIAN–TU); and studies of exercise and physical activity in preventing, treating, and managing Alzheimer's disease. Research is also being continued on support interventions for those caring for individuals with Alzheimer's disease and other dementias; for example, the NIA-funded REACH II intervention that is currently being broadly translated in 15 States through the Department of Veterans Affairs and in 3 States by the Administration on Aging.

Recently, NIA released 10 Funding Opportunity Announcements (FOAs). These FOAs incorporate themes and recommendations from the 2012 and 2015 Alzheimer's Disease Research Summits. They fall into seven broad categories, and offer opportunities for investigators in virtually every aspect of AD research—including health disparities, caregiving, epidemiology, diagnosis and prediction, molecular and cellular mechanisms, brain aging, and clinical trials. The FOAs have set-aside funds associated with them, and will be supported according to the availability of funds in fiscal year 2016 and fiscal year 2017.

Finally, while Alzheimer's disease is the most common form of dementia, related dementias, including vascular, frontotemporal, and Lewy body dementias, also represent a significant burden of dementia. Brain vascular disease such as silent stroke, diffuse white matter disease and arteriosclerosis is exceedingly common in persons with Alzheimer's dementia. The neurodegenerative processes can be difficult to distinguish clinically and frequently overlap. Research, too, is focused on neural processes that are shared among the different neurodegenerative disease and how aged blood vessels contribute to loss of brain function. For instance, increased funding for Alzheimer's and related dementia research allows researchers to begin sequencing DNA from 1,500 people with frontotemporal dementia and 1,300 people with Lewy body dementia to identify regions of DNA associated with risk for these disease and has enabled scientists to better understand the interactions between blood vessels, neurons, support cells, and proteins associated with Alzheimer's disease and how these interactions contribute to dementia.

IMPACT OF CR TO THE PRECISION MEDICINE INITIATIVE

Question. I know NIH has kicked off its precision medicine initiative, which has generated quite a bit of excitement. With the agency currently under a continuing resolution, what precision medicine efforts are currently being delayed by limitations on new starts and new efforts?

Answer. NIH efforts around the Precision Medicine Initiative (PMI) include both PMI Cohort Program, coordinated through the NIH Office of the Director (OD), and PMI for Oncology, coordinated through the National Cancer Institute (NCI). NIH OD is working diligently to implement the PMI Working Group's recommendations to build the PMI Cohort Program, developing funding opportunities, governance roles, and structures, and working to promote policies that are needed for the success of the PMI Cohort Program. These preparations are critical for ensuring that the PMI Cohort Program can begin its important work as soon as possible. Much of this planning can be done under the current continuing resolution, but a full-year continuing resolution would require us to put a halt to all of the PMI Cohort Program efforts. Similarly, NCI's PMI for Oncology has begun foundational work upon which it will build its PMI effort. By way of example, enrollment was open and highly successful for the NCI–MATCH trial, which will be dramatically expanded

under the PMI, adding more sites and adding more therapeutic agents, as well as speeding the development Pediatric MATCH. These planned expansions are jeopardized under the continuing resolution, slowing the progress of this critical trial.

FUNDING GRANTS DURING CONTINUING RESOLUTION

Question. The NIH has a set system for operating and dealing with its grant portfolio during a continuing resolution. Could you please describe the methodology you must implement when NIH does not have a full-year appropriation?

Answer. When NIH operates under a continuing resolution (CR) for part of the year, a Notice in the NIH Guide for Grants and Contracts is released describing the financial operations planned for grant awards during the CR (An example notice is NOT-OD-15-050, found at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-050.html). Generally, NIH's funding policy is to fund non-competing continuation awards at up to 90 percent of the committed award level, noting that reductions may be restored after an appropriation is in place. Since new, competing awards have not yet been committed, they are typically held until either appropriations legislation has been passed or, as in fiscal year 2011, a CR is approved to set funding levels through the end of the fiscal year. As a consequence, funding is delayed for highly meritorious new awards that are ready to be funded at the start of the fiscal year.

In fiscal years 2011–2015, more than three-fourths of NIH's new, competing grants were awarded in the third and fourth quarters when a final funding resolution or appropriation was in place. Thus, new, competing awards bear the brunt of funding delays. However, since yearly continuation award dates are linked to the date of the original, competing award, the practice of issuing multiple continuing resolutions affects the NIH funding cycle for the 4–5 year life of new awards issued in a given fiscal year.

NEURONEXT CLINICAL TRIALS

Question. The University of Kansas Medical Center is a site in the new NeuroNEXT clinical trials consortium. Can you tell us about the NeuroNEXT clinical trials program and how it has been a success in delivering clinical trials to neurology patients faster and more efficiently?

Answer. The NIH Network of Excellence in Neuroscience Clinical Trials was established in 2011 to provide shared infrastructure and centralized resources to expedite the development and execution of early phase clinical studies across a range of neurological disorders affecting adult and/or pediatric populations. To date, the network has initiated five clinical trials in five different neurological conditions and is streamlining the process of testing new therapies in patients.

The first study in the network completed enrollment ahead of schedule, and investigators are currently analyzing the data to identify early biological markers of spinal muscular atrophy (SMA) in infants. The raw data from this study will also be shared with the FDA in order to inform their ongoing evaluations of potential treatments for SMA. Three other trials are underway and are on target to complete enrollment on or ahead of schedule: one study is testing the safety and efficacy of a potential neuroprotective therapy in patients with progressive multiple sclerosis; another is exploring whether the drug rituximab can reduce the need for steroid use (which can have intolerable side effects) in patients with myasthenia gravis; and another is testing a new agent that has the potential to protect brain tissue in patients with moderate strokes who have been given the clot-busting drug tPA. The fifth study in the network was recently approved and will assess the tolerability of a new drug for treatment of aggression and irritability in patients with Huntington's Disease (HD), which are among the most distressing aspects of the disease.

NeuroNEXT has successfully engaged communities and partnered with private entities. Patient advocacy groups have been involved in all of the NeuroNEXT studies from early stage protocol development through the actual conduct of the study. The HD study is being conducted as a Small Business Innovative Research (SBIR) project, and the other studies have received contributions from private industry partners. The use of shared infrastructure and centralized expertise and resources, such as a single Institutional Review Board, has reduced inefficiencies and enabled the NeuroNEXT studies to achieve quicker start-up times than would have been possible in the traditional approach of establishing separate multi-site processes for each new trial. Further, their ability to consistently meet recruitment targets on schedule decreases clinical trial costs and facilitates on-time study completion. The expertise of the NeuroNEXT team and their ability to effectively recruit and partner across a broad range of neurology disciplines is reflected in the diversity of disorders and patient populations being addressed by the network.

PMI WORKING GROUP

Question. The PMI Working Group that Dr. Collins discussed in his QFR response has issued a report (which you probably have seen, but here it is for sake of convenience.[2] The Working Group recognized that excluding children would "limit the scientific validity and utility of the cohort, deprive PMI cohort participants of opportunities to benefit from research, and worse, could increase health disparities for these groups." The Working Group also recommended that the PMI—P include individuals from all life stages.

However, in reference to inclusion of special populations such as children, the Working Group noted that there are "scientific, ethical and policies issues surrounding these populations that warrant further discussion. Therefore, the Working Group recommends that NIH consider the safeguards necessary to ensure the appropriate enrollment, retention, and protection of these groups into the PMI cohort."

Considering these statements from the Working Group, could we get an update on NIH's plans for including a pediatric population within the PMI research cohort now that the Working Group has made recommendations?

Answer. NIH will include children as participants in the PMI Cohort Program. As recommended by the PMI Working Group, NIH is currently considering how to best incorporate pediatric participants into the cohort while fully addressing the unique scientific approaches and ethical commitments to this population.

Children present a unique set of legal, ethical and policy issues in clinical research that warrant careful consideration before actively recruiting them into the cohort. For example, existing Federal rules for the protection of research participants provide specific regulatory requirements for research involving children, including additional review by the Institutional Review Board and special consent procedures.[3] NIH is looking at an early pilot to enroll families as a way to test the best approaches to pediatric participation.

QUESTIONS SUBMITTED BY SENATOR THAD COCHRAN

CANNABIDIOL (CBD)

Question. At NIH, the Congress traditionally has allowed science to dictate how research dollars are spent. What is the potential utility of CBD-rich extracts in refractory childhood epilepsy (and perhaps other neurological disorders) and is the science there to justify the expenditure of Federal funds for research in this area?

Answer. There is evidence from small non-controlled (open label) studies that Cannabidiol-rich extracts may be effective in treating certain severe forms of childhood epilepsy in some individuals. Other studies have suggested that medical marijuana in various forms may relieve some symptoms of other neurological disorders. While these studies point to the promise of this research, they also highlight the need for rigorous studies to determine the safety and effectiveness of these compounds in treating neurological disorders, especially in children. Investigator-initiated research deemed meritorious through NIH's peer review process that follows applicable regulations would be an appropriate mechanism to help answer these important questions. The National Institute of Neurological Disorders and Stroke (NINDS) is currently conducting studies to investigate the anti-seizure activity of some of these compounds through NINDS's Anticonvulsant Screening Program (ASP), which offers academic and industry-based investigators the opportunity to screen compounds for anti-seizure activity in a battery of well-established rodent seizure models. Having obtained approval for appropriate Schedule 1 licenses, ASP is now collaborating with NIDA to conduct anti-seizure studies in rodents on Cannabidiol and tetrahydrocannabidiol (THC), the primary psychotropic compounds found in marijuana.

Question. If the science is there to justify CBD research, does NIH have sufficient funding for researchers to conduct these clinical trials?

Answer. In general, NIH does not set aside funding for research in a particular area, but rather funds the most meritorious investigator-initiated research—as determined by the NIH peer review process—across all the research areas within the NIH mission. Proposals for clinical trials are carefully reviewed to insure that there is sufficient pre-clinical research prior to testing potential therapies in humans. NIH

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[2] Http://www.nih.gov/precisionmedicine/09172015-pmi-working-group-report.pdf

[3] Please see the HHS Office for Human Research Protections guidance on subpart D of the HHS regulations at 45 CFR part 46 to learn more about regulations for research involving children at http://www.hhs.gov/ohrp/policy/faq/children-research/special-requirements-children-research.html.

welcomes investigator-initiated research on pre-clinical and clinical research on the promise of CBD for treating disease.

Question. Does NIDA's current contractor, the University of Mississippi, have the capacity to cultivate sufficient cannabis to meet researchers' needs and the ability to produce CBD under Current Good Manufacturing Practices (cGMP) for clinical research/trials?

Answer. The University of Mississippi has been able to meet the supply demands of the scientific community for marijuana thus far; however, interest in marijuana research is rapidly growing and researchers are interested in many diverse strains of marijuana including strains with high levels of CBD. While the NIDA contractor could increase the volume of marijuana grown and available it would be impractical for NIDA to produce, at this single facility, more than a few of the varieties of marijuana currently being used in the various States. This has led some to argue that it is important to license additional growers of marijuana for research purposes. Federal agencies including HHS, the Department of Justice (DOJ), the Office of National Drug Control Policy (ONDCP) and the State Department have been working together to identify potential solutions to this issue that are in compliance with U.S. laws and international treaty obligations.

Currently, the NIDA Drug Supply Program does supply CBD for animal research purposes, and the University of Mississippi has developed a marijuana extract with a high concentration of CBD under cGMP procedures. This extract is available for human research studies; however, the current formulation is not conducive for easy administration within human clinical trials. Researchers interested in using this extract for human studies would need to develop a formulation for easy administration (e.g., oral suspension in sesame oil). NIDA is currently working with the FDA to develop easy-to-use formulations and dosages of this extract for human research.

In addition, NIDA recently awarded an SBIR to Aphios to develop a method for generating cGMP grade CBD for use in clinical trials and other research projects. The primary goal of this research program is to develop a process for manufacturing pharmaceutical grade CBD following current cGMP of the FDA for use in clinical trials for childhood epilepsy and other indications. The secondary goal is to develop a standardized, enriched CBD product for use in clinical trials. Having additional suppliers of both marijuana plant products and purified CBD would ensure that these products are available to scientists in a more timely fashion.

Question. If there is both the capacity to cultivate sufficient amounts of cannabis and the ability to produce CBD under cGMP at the University of Mississippi, is the barrier to production due to a lack of funding within NIDA?

Answer. The University of Mississippi has been able to meet the supply demands of the scientific community for marijuana thus far.

IDEA PROGRAM

Question. The Mississippi IDeA Network of Biomedical Research Excellence links colleges and universities across the State in order to engage our talented researchers and students in research projects. NIH's investment in the IDeA program, which benefits almost half the States in the Nation, is relatively modest compared to the overall NIH budget. Do you plan to invest more in the IDeA program in the future and what are your strategies for continuing to ensure the success of this program?

Answer. NIH appreciates the Committee's support for the Institutional Development Award (IDeA) program and recognition of the importance of the goals of providing research infrastructure and building research capacity in the IDeA institutions. In fiscal year 2016, NIH anticipates making 12 new Center of Biomedical Research Excellence (COBRE Phase I) awards and supporting up to 8 COBRE competing continuation (Phase II) awards and 6–7 new COBRE Phase III awards. Twenty-three IDeA Network of Biomedical Research Excellence (INBRE) awards have competed successfully for continued support. NIH anticipates making one additional competing continuation INBRE award and 4 new IDeA–CTR awards. NIH also anticipates co-funding 25 R01 and R15 awards across NIH Institutes and Centers. Additionally, support will be provided for the non-competing COBRE, Institutional Development Award Program Infrastructure for Clinical and Translational Research (IDeA–CTR), and INBRE awards that constitute the IDeA base.

To ensure the success of this program, NIH plans to:

—Continue to build active biomedical research environments in IDeA States and improve access to modern, state-of the-art biomedical research for students, researchers, and the general public in IDeA States.

—Ensure that States without medical schools have an opportunity to develop research capacity for conducting basic, translational and clinical research.

—Continue to provide opportunities to address health disparities in medically underserved groups residing in IDeA States.
—Continue promoting the Small Business Innovation Research/Small Business Technology Transfer programs, technology transfer, entrepreneurship, and public-private partnerships to create and enhance vibrant translational research environments within IDeA supported institutions.
—Encourage collaborations and leveraging among IDeA research resource centers to capitalize on each other's unique capabilities to solve complex research queries, and encourage consolidation of research resources that hold complementary technologies to improve efficiency and create economies of scale.
—Enhance the competitiveness of institutions by providing opportunities for talented undergraduate students to participate in research training and research careers in the biomedical sciences.

Develop best practices, training tools, workflows, databases, and analysis tools that assist clinical and translational researchers to develop and perform clinical and translational protocols to quickly and efficiently address important questions in multiple areas of science.

LEVERAGING EXISTING ALZHEIMER'S RESEARCH

Question. The University of Mississippi Medical Center serves as a study site and conducts research in the Atherosclerosis Risk in Communities (ARIC) Neurocognitive Study. This study is the most comprehensive research project currently funded by NIH that examines risk factors for dementia. How do you plan to maximize the potential of existing research studies, like ARIC, as NIH moves forward with the BRAIN initiative?

Answer. The Atherosclerosis Risk in Communities Study (ARIC) is a prospective study of almost 16,000 participants in four U.S. communities that is exploring the causes and consequences of atherosclerosis, and how cardiovascular risk factors, medical care, and disease vary by race, gender, location, and date. Extensive medical, social, and demographic information was collected on the participants through five in-person examinations over 25 years, and their health status continues to be followed annually by phone. The ARIC Neurocognitive Study is investigating the role of midlife vascular risk factors in dementia and cognitive impairment, and how the burden of these conditions varies by race and sex. Cognitive testing has been conducted to assess decline in cognitive ability, executive function, memory, and language skills, and brain MRI has been performed to detect abnormalities known to be associated with cognitive impairment. These studies have led to the finding that high blood pressure in midlife was associated with cognitive decline in later life, results that were demonstrated in a recent publication (Gottesman et al., 2014. JAMA Neurol; 71(10): 12181227). An additional ancillary study to ARIC is the PET-Amyloid Imaging Study, which is conducting specialized brain imaging on some of the participants to better understand the link between vascular risk factors and hallmark characteristics of Alzheimer's disease that can be seen on amyloid imaging, and how their prevalence associates with development of dementia. The ARIC study provides an important opportunity to study potentially modifiable risk factors for dementia over a long period of time and thus could have important implications for public health.

In addition to large-scale observational studies such as ARIC, research conducted through the Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative also holds potential to advance dementia research. A patient's symptoms are the manifestation of dysfunction in brain circuit activity, yet currently available tools for monitoring and modulating brain circuits are inadequate for fully understanding the basis for neurological and mental disorders. The BRAIN Initiative promises to deliver new technologies that will amplify our ability to monitor and therapeutically change brain circuit activity, leading to a new understanding of how individual cells and complex neural circuits interact in both normal and disordered conditions. Advances in neuroimaging technologies in particular will enhance our ability to study dementia and other brain disorders more effectively. Unprecedented opportunities will emerge from these advances to pursue new ways to treat a wide range of brain disorders, including dementia, and in combination with the wealth of knowledge we are gaining from studies like ARIC NCS, the research community will be well poised to translate these discoveries into improved public health.

QUESTIONS SUBMITTED BY SENATOR MARK KIRK

BATTEN DISEASE

Question. One of the cities I represent has been gripped by the story of Charlotte and Gwenyth Gray, two beautiful young girls diagnosed with Batten Disease, a neurodegenerative brain disease that will leave them blind, immobile, cognitively impaired and eventually dead between the ages of 6 and 12. A disease for which currently there is no treatment or cure. This community, that I am proud to represent, recently came together to raise $350,000 for research to cure Batten, trying to beat the clock for Charlotte and Gwenyth and believing that no other parents and children should have to face this horrible disease and deadly outcomes. However, as you well know, the funds that can be raised privately pale in comparison to the Federal disease research infrastructure. What can NIH do to assist researchers racing to help children with Batten Disease?

Answer. NIH assists researchers racing to help children with Batten disease directly by supporting their research. NIH also supports the development of research tools, resources, and basic research that underpins progress against many diseases, including Batten disease. For example, researchers studying Batten disease have applied genetic technologies, online genetics databases, and informatics tools developed through NIH support to identify specific gene defects that cause Batten disease. They have used methods from NIH investments in basic stem cell biology to develop induced pluripotent stem cells derived from skin cells of patients with Batten disease that enable them to study crucial aspects of the disease in cell culture and to screen for potential treatments. And they have capitalized on advances in genetic engineering to produce transgenic mouse models of Batten disease to study the disease and test interventions. Likewise, researchers developing candidate therapeutic interventions for Batten disease rely on more general progress in gene therapy, stem cells, biomarkers, imaging technologies, and methods to, among other example, provide access of therapeutic agents through the blood brain barrier. For example, studies are underway to advance gene therapy for Batten's disease using viral vectors to deliver the missing enzyme.

Question. And how can this orphan disease and others like it, get the Federal grant funding they need to make a difference for children?

Answer. Because of the devastating effects of Batten disease on the brain, the National Institute of Neurological Disorders and Stroke (NINDS) leads NIH research against this disease. Other parts of NIH support research and bring their expertise to bear as appropriate to their missions; for example, the National Eye Institute (NEI) supports research on blindness caused by this disease. NINDS, like all of NIH, places a high priority on supporting research against rare disorders because the private sector is less likely to invest in rare diseases and rare disorders provide crucial clues to more common diseases. Most importantly, rare diseases have an enormous impact on families. NINDS provides a wide array of different types of grants suitable for all types of investigator-initiated research on rare diseases, from early exploratory research to in-depth studies, and from basic research on disease mechanisms through preclinical therapy development and clinical trials. The NeuroNext clinical trial network was designed specifically to serve the needs of clinical research in rare pediatric neurological diseases, such as Batten disease, as opportunities emerge. Private advocacy groups play a very important role in encouraging researchers to take up the challenge of Batten disease and other rare diseases, and NINDS scientific program directors guide investigators to take advantage of these funding opportunities. Currently funded grants related to Batten disease include pilot projects, traditional R01 grants, and multi-investigator projects, and range from basic studies to understand how gene defects cause harm, though early preclinical therapy development using a variety of strategies, and clinical studies in patients to develop advanced MRI and laboratory tests to objectively measure the progress of the disease and whether patients are responding to therapies. The NIH RePORT website (https://projectreporter.nih.gov/reporter.cfm) provides access to summaries and links to published results from current and past grants on Batten disease.

INDUCED PLURIPOTENT STEM CELLS

Question. How are induced pluripotent stem cells being used in laboratories at NIH to advance biomedical research? To what extent has this research led to new treatments or cures?

Answer. Recent research has demonstrated that stem cells have the remarkable potential to develop into many different cell types in the body. In many bodily tissues, stem cells serve as a kind of internal repair system, dividing extensively to

replenish other cells as long as the person or animal is alive. When a stem cell divides, each new cell has the potential either to remain a stem cell or become another type of cell with a more specialized function, such as a muscle cell, a red blood cell, or a brain cell. A recently developed research technique, which garnered the 2012 Nobel Prize in Physiology or Medicine, now makes it possible to create a new type of stem cell called an induced pluripotent stem (iPS) cell in the laboratory. iPS cells are derived from mature cells, typically from a patient's skin or blood, which researchers can reprogram back to an immature state. These cells can then be turned into a wide variety of cell types, including liver cells, neurons, cardiac cells, and blood cells. NIH-funded scientists are studying iPS cells and other types of stem cells, not only to understand better cell function and disease pathways, but also to develop therapies for a variety of diseases and disabilities, including Parkinson's disease, amyotrophic lateral sclerosis (ALS), spinal cord injuries, heart disease, diabetes, and arthritis. Since the development of iPS cells is a relatively new discovery, most NIH funded research is focused on finding ways to develop different cell types from iPS cells, refining methods so that the resulting cells would be safe to use in people, and testing the cells in animal models. Three examples are given here of promising approaches:

—Macular degeneration: an NIH intramural scientist is pursuing preclinical efficacy and safety studies with retinal pigment epithelium tissue, developed from a patient's own skin cells using iPS technology, to treat age-related macular degeneration, a leading cause of blindness in the elderly.

—Type 1 diabetes: NIH-funded researchers at Harvard University developed a multistep process to coax large numbers of both iPS cells and human embryonic stem cells into a state that closely resembles naturally-occurring pancreatic beta cells, with the ability to respond to fluctuating glucose levels by appropriately increasing or decreasing secretion of insulin. Two weeks after transplantation into a mouse model of type 1 diabetes, these stem cell-derived beta cells were still able to produce significant amounts of insulin in response to glucose and protect against hyperglycemia. Although the process will need to be adapted for large-scale manufacturing, and further tests must be conducted to determine if stem cell-derived beta cells can be a long-term replacement for beta cells in people, this dramatically improved process for making large amounts of beta cells is a promising step toward developing therapeutic stem cell therapies; it may also lead to advances in artificial organ development.

—Liver failure: NIH-funded researchers at the University of California, San Francisco and the Gladstone Institutes have coaxed iPS cells into becoming what appear to be fully functional liver cells. They have developed a protocol that transforms human skin cells into mature liver cells that not only function normally in a lab dish, but proliferate after they have been transplanted into mice that model human liver failure. This ability to proliferate is a hallmark of normal liver cells—and the secret to the liver's astounding capacity to regenerate after infection or injury.

QUESTIONS SUBMITTED BY SENATOR BILL CASSIDY

HIV FUNDING

Question. As was asked during the Appropriations Hearing on October 7, 2015, in fiscal year 2014, the National Heart, Lung, and Blood Institute (NHLBI) received $64,044,000 from the Office of AIDS Research (OAR) (or 2.1 percent of all the AIDS Research funding at NIH) to study heart, lung, and blood disease co-morbidity with HIV. After much research, we learned from the American Heart Association that in 2013, the CDC reported an incidence of 1,815 cardiovascular disease deaths with HIV as the underlying cause. CDC also reported that about 610,000 Americans die from cardiovascular disease every year. Of those who die from cardiovascular disease each year, only .29 percent of them have HIV as underlying cause—that is very low. During the meeting of the National, Heart, Lung, and Blood Advisory Committee in 2012, it was reported that the success rates for AIDS application that were much higher than for non-AIDS applications—42 percent vs 18%—suggesting that projects with low review scores and low significance are being funded. Please provide answers to the following related questions:

—What are the success rates for HIV related applications at the other NIH Institutes that receive OAR funding?

—What are the success rates for non-HIV applications at Institutes?

Answer. NIH Institutes and Centers provide AIDS funding to unsolicited investigator-initiated grant applications and applications submitted in response to specific

funding opportunity announcements (FOAs) that are deemed highly meritorious in NIH's dual level peer review process. Applications awarded under a FOA targeted to a specific scientific topic or objective may appear to have an unusually high success rate, but this is not because projects with low review scores and low significance are being funded; on the converse, targeted FOAs sometimes attract a small number of applications prepared by applicants who are exceptionally qualified to address the objectives of the FOA, and a larger proportion of these applications are deemed to be highly meritorious in the peer review process.

The success rate indicates the percentage of reviewed grant applications that were awarded on a fiscal year basis. It is determined by dividing the number of competing applications funded by the sum of the total number of competing applications reviewed and the number of funded carryovers. The success rate calculation is always performed after the close of the fiscal year. To better reflect the funding of unique research applications, the number of grant applications is adjusted by removing the number of revised applications and correcting for projects where the resubmitted application is submitted in the same year as the original grant application.

NIH supports a comprehensive program of biomedical, behavioral, and social science research on HIV/AIDS and its associated comorbidities, coinfections, and other complications. As therapeutic approaches to managing patients with HIV/AIDS have improved, so has the longevity of patients who can tolerate the side effects, toxicities, and other complications associated with the treatment regimens. As a consequence, there also is an increasing occurrence of HIV-associated comorbidities, including cardiovascular, hepatic, metabolic, renal, neurologic, AIDS-defining, and non-AIDS defining malignancies, and other clinical complications associated with long-term HIV disease and antiretroviral therapy. An overarching priority for the NIH HIV/AIDS research program is the prevention and treatment of HIV-associated comorbidities and coinfections.

The clinical challenges confronting HIV-infected patients on optimal antiretroviral therapy is shifting from acute infectious complications associated with HIV to chronic diseases, such as coronary artery disease, chronic lung disease, and chronic anemia. By 2030, it is estimated that 84 percent of the HIV population will have one or more co-morbidities, and 78 percent will have cardiovascular disease. Research findings also suggest that HIV-infected individuals are up to twice as likely as those without HIV to have cardiovascular disease, yet this important public health issue remains understudied. What we learn about HIV-related inflammation and other pathophysiological processes may provide insights into all patients with cardiovascular disease.

—The success rates for each NIH Institute and Center's HIV-related research project grant applications in fiscal year 2014 is provided in the table on the next page. The trans-NIH success rate for HIV-related research project grants was 22.9 percent in fiscal year 2014.[4]

—The trans-NIH success rate for all applications was 21.0 percent in fiscal year 2014.

The success rates for each NIH Institute and Center's research project grant applications in fiscal year 2014 is provided publically at: http://report.nih.gov/DisplayRePORT.aspx?rid=601.

HIV/AIDS-RELATED SUCCESS RATES FOR RESEARCH PROJECT GRANT APPLICATIONS BY NIH INSTITUTES AND CENTERS IN FISCAL YEAR 2014 [5]

Institute/Center	Success Rate
NCI	17.9%
NHLBI	41.2%
NIDCR	28.6%
NIDDK	13.1%
NIGMS	100.%
NICHD	17.1%
NEI	.....
NIEHS	.....

[4] Research Project Grants are defined as activity codes R00, R01, R03, R15, R21, R22, R23, R29, R33, R34, R35, R36, R37, R55, R56, RC1, RC2, RC3, RC4, RF1, RL1, RL2, RL5, RL9, P01, P42, PN1, PM1, RM1, UA5, UC1, UC2, UC3, UC4, UC7, UF1, UH2, UH3, UH5, UM1, UM2, U01, U19, U34, DP1, DP2, DP3, DP4, and DP5. Not all of these activities may be in use by NIH every year.

HIV/AIDS-RELATED SUCCESS RATES FOR RESEARCH PROJECT GRANT APPLICATIONS BY NIH INSTITUTES AND CENTERS IN FISCAL YEAR 2014 [5]—Continued

Institute/Center	Success Rate
NIAID	13.6%
NIAMS	.....
NIDCD	100.%
NIMH	11.6%
NIDA	23.4%
NIAAA	14.1%
NINR	20.%
NHGRI	.....
NIBIB	7.1%
NIMHD	.....
NCCIH	.....
NCATS	.....
FIC	9.1%
NLM	.....
ORIP	100.%
Total NIH	22.9%

[5] Research Project Grants are defined as activity codes R00, R01, R03, R15, R21, R22, R23, R29, R33, R34, R35, R36, R37, R55, R56, RC1, RC2, RC3, RC4, RF1, RL1, RL2, RL5, RL9, P01, P42, PN1, PM1, RM1, UA5, UC1, UC2, UC3, UC4, UC7, UF1, UH2, UH3, UH5, UM1, UM2, U01, U19, U34, DP1, DP2, DP3, DP4, and DP5. Not all of these activities may be in use by NIH every year.

QUESTIONS SUBMITTED BY SENATOR PATTY MURRAY

NIH CENTERS FOR ACCELERATED INNOVATIONS

Question. Please provide an update on the NIH Centers for Accelerated Innovations (NCAI) program and any progress the initiative has made in addressing the gap in the commercialization pipeline between scientific discovery and moving breakthrough innovations. Are any NIH institutes considering hosting a similar concept with their funds?

Answer. The National Heart, Lung, and Blood Institute (NHLBI) established the NIH Centers for Accelerated Innovations (NCAI) as a pilot program to identify emerging technologies in the academic laboratory research setting and facilitate their transition into commercial products that can improve patient care and enhance health. Launched in September 2013, the three Centers merge the strengths of 15 high-impact research institutions with expertise and resources from both Federal and private-sector partners. The NHLBI committed $35.5 million over 7 years to the NCAI program, and the Centers have raised non-Federal matching capital to leverage this Federal investment.

To accomplish their goals, NCAIs support proof-of-concept studies, educate academics on the technology development process, and provide early access to the scientific and business expertise needed for commercialization. NCAIs provide early mentoring to innovators to develop key business elements (legal, business development, regulatory, reimbursement, access to partners and capital), which are often not well understood by academic scientists and are critical for commercial success of developed technologies. Innovator response to the program has been robust, and the Centers received a wide range of applications to develop devices, therapeutics, diagnostics, and tools to address a broad spectrum of heart, vessel, lung, blood, and sleep disorder and diseases.

Over the past year, efforts to address the gap in the commercialization pipeline between scientific discovery and commercialization were expanded in two ways. First, the National Institute on Drug Abuse joined the NCAI program and committed $3 million to support innovator education and technologies targeted to substance abuse at one of the three centers. Second, the NCAI model was scaled across NIH through a new, 3-year trans-NIH, $9 million dollar Research Evaluation and Commercialization Hub program (REACH). Working in concert, the NCAI and REACH programs will enable development of self-sustaining biomedical technology development ecosystems that encourage the conversion of laboratory discoveries into products and services and disseminate best practices for technology development to other agencies, institutions, and regions across the Nation. NIH will closely evaluate both of these programs as they are completed. By moving innovative technologies into the private sector for patient benefit, this network will enhance the commercial outcomes of federally-funded research for health, societal, and economic benefit.

BRAIN INITIATIVE

Question. What has been the average amount of funding for grants awarded to date through the BRAIN initiative?

Answer. The average award amount for grants funded by NIH through the BRAIN Initiative is approximately $650,000 annually per award. Most are 3-year grants.

Question. Should the additional funding requested for BRAIN be provided in fiscal year 2016, would NIH expect to use a portion of these funds to support significantly larger awards to tackle bigger challenges facing the initiative?

Answer. In short, yes. The BRAIN Initiative is focused on understanding the functions of specific brain circuits, including circuits relevant to Parkinson's disease, epilepsy, recovery from traumatic brain injury and stroke, mental illnesses, and addiction. Understanding this circuit functionality in the human brain is a critical goal highlighted by the external scientific advisors that developed BRAIN 2025, the roadmap for NIH's portion of the BRAIN Initiative, and one that is echoed by the BRAIN Multi-Council Working Group, another group of esteemed external neuroscience experts that provides ongoing oversight of the long-term scientific vision of the NIH BRAIN Initiative. This goal is also a major challenge facing the Initiative, and starting in fiscal year 2016, NIH would like to greatly expand its BRAIN research investments on understanding human brain circuit function. Such research includes both invasive studies, which will make use of latest-generation brain stimulating and/or recording devices, as well as research with noninvasive devices for modulating brain function, which do not require surgery and do not penetrate the brain (for example, transcranial magnetic stimulation with a magnetic coil). These non-invasive devices are rapidly being developed and could become an alternative or an adjunct to current therapies for various brain diseases and disorders.

To support this expansion into human brain research, the awards are likely to be larger than prior NIH-funded BRAIN grants. This is partly due to the cost of doing research with human subjects, and partly because NIH has focused much of its current BRAIN investment in smaller planning grants and other types of preliminary, exploratory awards aimed at developing new technologies and tools. Nevertheless, it will be important for NIH to continue supporting a wide range of BRAIN investigators and while some awards will likely be larger as described, NIH will still likely continue support of smaller, exploratory, high risk projects in various areas, under the continued direction of the BRAIN Multi-Council Working Group.

QUESTION SUBMITTED BY SENATOR JACK REED

IDEA PROGRAM

Question. What is NIH doing through IDeA and other initiatives to help States like Rhode Island become more competitive for Federal research dollars so that we don't wind up concentrating our investments in the same institutions and geographic areas?

Answer. The Institutional Development Award (IDeA) program is designed to enhance the research infrastructure and increase the research capability and competitiveness of investigators in institutions located in States with historically low aggregate grant awards from NIH. Grant awards are made to independent biomedical research institutions that award doctoral degrees in the health sciences or sciences related to health within IDeA-eligible States and to research institutes. The primary objectives of the IDeA program are to develop research capacity and broaden the geographical distribution of NIH funding, ensuring that cutting-edge biomedical research is conducted throughout the Nation.

The IDeA program continues to strive to meet its primary goal of providing for biomedical research capacity across all of the IDeA-eligible States and to distribute its resources broadly and appropriately to support cutting edge biomedical research that serves the needs of the medically underserved populations in these regions. The program continues to support competing (new and renewal) and non-competing Center of Biomedical Research Excellence (COBRE) and IDeA Network of Biomedical Research Excellence (INBRE) awards that constitute the IDeA base. Additionally, support is provided for IDeA Program Infrastructure for Clinical and Translational Research (IDeA–CTR) awards and continued co-funding of Independent Research Project (R01 and R15) awards solicited from across the NIH Institutes and Centers (ICs). In fiscal year 2015, the National Institute of General Medical Sciences (NIGMS) supported 23 INBRE awards, 54 Phase I/II and 46 Phase III COBRE awards, and 5 IDeA–CTR awards. In fiscal year 2015, IDeA co-funded 25 R01/R15 awards to 18 NIH ICs.

NIH will continue to support new competing Phase I COBRE awards, as well as Phase II and Phase III COBRE awards. Funds will be provided to support competing INBRE applications. Additionally, NIH anticipates supporting new IDeA–CTR awards.

In terms of collaboration and shared funding from outside NIGMS sources, NIH ICs are taking increasing interest in and are working with the IDeA program. For instance, the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) is working with IDeA program staff to develop two funding announcements to support Pediatric Clinical Research Networks in IDeA States. A proposed Data Coordinating and Operations Center (DCOC) will support the activities of the IDeA States Pediatric Clinical Research Network (ISPCRN). The funded DCOC will cooperate with the IDeA Program Directors/Principal Investigators to train pediatric clinical trial teams. These teams will utilize existing infrastructure and networks put in place by the IDeA program in these States to support new research paradigms to address pediatric health, particularly in rural and underserved communities. These initiatives, developed by NICHD in conjunction with NIGMS, will be supported by funds from the NIH Office of the Director.

IDeA program staff have engaged the Director of the Division of Extramural Research at NIDCR in exploring ways to inform dental schools in IDeA States about the funding opportunities for COBRE Phase I awards. The possibilities discussed were a webinar or having information available at the NIDCR booth in the dental research meeting. The NIDCR Director will consult with senior staff at that institute.

NIGMS and other ICs will continue to support, through co-funding, meritoriously reviewed research projects that have not made the pay lines of the other ICs. The IDeA Director sends out solicitations to all the ICs for meritorious applications for nomination of co-funding by the IDeA program.

Six IDeA States have Clinical and Translational Science Awards and institutions in IDeA States continue to be eligible to compete for these awards. NIGMS is speaking with staff from the National Center for Advancing Translational Sciences to promote this idea.

Lastly, NIGMS is also considering options to set up biotechnology accelerators in each of the four IDeA regions to facilitate translating basic discoveries to marketplace, as directed by the Senate (Senate LHHS report 2016, page 92).

QUESTIONS SUBMITTED BY SENATOR BRIAN SCHATZ

TOBACCO TO 21

Question. Tobacco prevention and control is one of the most cost-effective public health interventions we can use as policymakers to prevent unnecessary tobacco deaths. In March, the Institute of Medicine concluded that raising the minimum legal age of sale of tobacco products would result in 223,000 fewer premature deaths, 50,000 fewer deaths from lung cancer, and 4.2 million fewer years of life lost for those born between 2000 and 2019. It would also reduce tobacco initiation, especially among youth 15 to 17 years old. That's why I introduced S. 2100, the Tobacco to 21 Act with nine of my Senate colleagues, which would raise the minimum legal age of sale of tobacco products to 21.

The NIH has a Tobacco Regulatory Science Program that coordinates the trans-NIH collaborative effort with the FDA's Center for Tobacco Products to do research and support its tobacco regulatory activities. I am also aware that the NIH funds numerous studies on tobacco and nicotine use and their impacts on public health.

I have two questions for Dr. Collins and Dr. Lowy, in particular, regarding tobacco research:

1. Has NIH studied the relationship between increasing the minimum legal age of sale of tobacco products and an improvement in public health? What were the results of that research? And what would you expect from increasing the minimum legal age of sale of tobacco products from 18 to 21?

2. What are other demonstrated successes from a research perspective in the effort to prevent and control tobacco deaths? Do you have data on deaths averted and lives saved thanks to these preventive efforts, and/or data on cost-effectiveness of these efforts?

Answer. The Institute of Medicine (IOM) released the report, Public Health Implications of Raising the Minimum Age of Legal Access to Tobacco Products, in March 2015. The report was commissioned by the Food and Drug Administration (FDA) to specifically address the questions noted here in part a. That report used statistical modeling and other methods to determine its findings. Specifically, the report con-

cluded that, based on modeling, raising the age of legal access to tobacco products, particularly to age 21 or 25, will likely lead to substantial reductions in smoking prevalence and smoking related mortality. The report also concluded that, based on a review of the literature and on modeling, that an increase in the minimum age of legal access to tobacco products will likely improve maternal, fetal, and infant outcomes by reducing the likelihood of maternal and paternal smoking.

One of the two statistical models that informed the IOM findings is NCI's Cancer Intervention and Surveillance Modeling Network (CISNET) smoking population model, which simulates annual age-specific smoking prevalence and smoking-attributable mortality. NCI also provided support for the SimSmoke modeling of the potential impact of increasing the minimum age of sale on birth outcomes. As of this time, NCI has not funded other research on the potential impact of increasing the minimum legal age of sale of tobacco products. NCI concurs with the IOM report's findings that raising the minimum legal age of sale of tobacco products would likely result in a reduction in the prevalence of tobacco use and a reduction in disease, including cancers, caused by tobacco use.

NIH, including NCI and other Institutes and Centers, supports a broad-based portfolio of tobacco control and prevention research. This research continues to contribute to the evidence base for understanding and reducing tobacco use among youth and adults. Successful strategies to reduce tobacco use include mass media campaigns, raising taxes on tobacco products, comprehensive smoke-free air laws, efforts to promote non-smoking norms, and barrier free access to evidence-based smoking cessation treatment. Over many decades, these and other programs and policies have contributed to substantially reducing smoking prevalence and smoking-caused disease. For example, a study conducted by NCI CISNET investigators estimated that twentieth-century tobacco control programs and policies averted nearly 800,000 deaths from lung cancer between 1975 through 2000.[6] Similarly, NCI supported researchers determined that the long-running California tobacco control program reduced smoking prevalence and per capita cigarette consumption; this research also estimated that between 1989 and 2008, the California tobacco control program cost $2.4 billion, but led to approximately $134 billion in healthcare expenditures savings.[7]

Despite significant progress in reducing the prevalence of tobacco use in the United States, and the incidence of tobacco related cancers, tobacco use continues to represent a major threat to public health. In addition, decreases in tobacco use have not been consistent across the population and prevalence remains high among certain groups. For this reason, NCI supports a broad range of research on the etiology, prevention, treatment, and control of tobacco use.

Additionally, within the framework of the Family Smoking Prevention and Tobacco Control Act, signed into law in 2009, the NIH and FDA's Center for Tobacco Products (CTP) formed an interagency partnership to foster tobacco regulatory research. NIH biomedical, behavioral and social sciences research supported in partnership with FDA is providing the scientific evidence needed to inform FDA's regulatory authorities.

In collaboration with the NIH Tobacco Regulatory Science Program, NCI is developing an evidence base to inform the FDA CTP regulatory authority over the manufacture, marketing, and distribution of tobacco products in order to protect public health. Although a vast and sound scientific evidence base exists to support the Tobacco Control Act, new research will provide scientific evidence in several areas. This includes research to better understand e-cigarettes and other tobacco products (initiation, use, perceptions, dependence, toxicity), and the impact of tobacco product characteristics on initiation, especially among youth and other vulnerable populations.

TELEHEALTH AND MHEALTH

Question. As I've talked about before, I am a strong believer in Telehealth, including mobileHealth or mHealth, and remote patient monitoring as a way to improve healthcare quality and access, and decrease costs.

The VA, DOD, and private insurers have well defined protocols and standards for delivery of Telehealth. However, there are many restrictions on Medicare reimbursement of Telehealth in the 1834(m) statute under the Social Security Act which I am working with my colleagues to address.

Dr. Collins, how is the NIH engaged on research to demonstrate the efficacy and cost-effectiveness of Telehealth? What initiatives are you pursuing?

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[6] Http://www.cancer.gov/news-events/press-releases/2012/TobaccoControlCISNET.
[7] Http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3572143/.

Answer. Listed below are NIH activities related to Telehealth and mHealth.

NIH's Extramural activities—Telehealth, including mobile health (mHealth), is well represented in the extramural funding of the various NIH institutes and centers with over 200 awarded projects in fiscal year 2015. See selected examples below:

—*Randomized Trial of an Innovative Smartphone Intervention for Smoking Cessation*.—With over 400 smoking cessation mobile applications being downloaded millions of times in the United States over 2012–2013, there is a need for systematic, rigorous evaluation of the effectiveness of cessation intervention trials. This randomized trial will utilize an approach, called Acceptance & Commitment Therapy (ACT), which has a dual focus on subjects increasing willingness to experience physical cravings, emotions, and thoughts that cue smoking while making values-guided committed behavior changes. If effective, the smartphone application will provide a cost-effective intervention with maximal population-level impact.

—*Perinatal Nurse Home Visiting Enhanced with mHealth Technology*.—The Institute of Medicine, World Health Organization and Centers for Disease Control and Prevention recognize that prenatal home visitation, which improves the well-being of mother and children, presents an opportunity to provide early intervention to reduce intimate partner violence (IPV), and the impact the exposure has on the children. This study will utilize mHealth technology which aims to increase the sensitivity of screening instruments and reduce communication barriers between nurses and clients regarding IPV, as well as enhance and standardize the implementation of IPV interventions.

—*A personal exposure and response monitoring system for pediatric asthma study*.—This study will develop a button-sized device that can monitor asthma triggers (chemicals and particulate matter) and physiological signals of a child 24 hours a day. This system can potentially impact the epidemiological study of the pollution exposure-response relationship, and eventually the prevention of pediatric asthma. The project will bring together strengths in chemical sensors, particulate matter detectors, epidemiology, and digital health from different groups, as well as industry collaborators.

—*Dynamic, real-time prediction of alcohol use lapse using mHealth technologies*.—Despite the effectiveness of available psychosocial and pharmacological treatments to establish abstinence for patients with alcohol use disorder, the vast majority of patients relapse within a year and often within the first few months following treatment. The goals of this project are to develop, validate, preliminarily optimize, and deliver a dynamic, real-time lapse risk prediction model for forecasting alcohol use among abstinent alcoholics. This lapse risk prediction model will be integrated into an existing validated mHealth platform to encourage sustained recovery through adaptive use of continuing care services.

To facilitate rigorous research in mobile health, the Office of Behavioral and Social Sciences Research (OBSSR) has engaged in a number of funding opportunity announcements and training activities. For the past few years, OBSSR has led a number of NIH mHealth training sessions which bring together biomedical and behavioral researchers and computer scientists and engineers to learn skills in developing and evaluating mobile health applications. In fiscal year 2015, OBSSR, NIBIB, and other partner institutes awarded a mobile health research resource to the University of California San Francisco (1U2CEB021881) that will provide researchers with a large test bed of mobile phone users and the resources to encourage rigorous mobile health research. NIH also recently released a competitive supplement funding announcement to encourage current NIH grantees to incorporate and test new mobile and Telehealth technologies in their research.

NIH Intramural Activities.—NIH's Center for Information Technology (CIT) is one of the NIH Intramural Research Program leaders in Telehealth and mHealth. CIT created an extensive Telehealth program for NCI that connected a number of cancer centers in major hospitals in the United States and abroad (e.g., Ireland and Jordan) to allow collaboration on difficult cancer cases. This system, called TELESYNERGY®, provided real time multi-center collaboration and included high resolution imaging capability. In 2006, CIT adapted for NIDDK, TELESYNERGY® to create a telemedicine clinic that runs in conjunction with the Indian Health Service's Zuni Indian Hospital. This clinic meets regularly, and NIH CIT provides technical support as needed.

More recently, NIH CIT created mHealth iPad application called the mICU Clinical Information System (CIS) App, which allows the NIH Critical Care Medicine Department staff to quickly ascertain the status of patients in their Critical Care Unit. This application has been approved to be interfaced with the Clinical Center's Clinical Research Informatics System (CRIS), so that it can go online when con-

nected, providing a major upgrade in functionality to the CRIS system. Finally, the Radiation Research Program at NCI is interested in an updated version of TELESYNERGY® that can be deployed via an iPad to physicians in rural areas or undeveloped countries. These iPads would connect to servers in the closest major hospitals and provide physicians access to more specialized diagnosis and treatment options that might not otherwise be available. NIH CIT also is beginning to develop two new mHealth applications, an iPad App for the Connectome project in collaboration NINDS and an iPhone App, to study teen driving habits with NICHD.

A number of other ICs have started or are planning to start programs in these areas. On October 22, 2015, NIH had its first mHealth Interest Group meeting. There is a great deal of enthusiasm in this new interest group. Roughly 14 NIH ICs have expressed an interest in participation in this newly formed group.

NIDA Intramural Research Program Treatment Section aims to realize the full breadth of possibilities for mHealth, seeking results that can apply not only to substance-use disorders, but to any health condition with behavioral and environmental-exposure components. Methods for ambulatory assessment combine real-time self-report, continuous physiological monitoring, and continuous geospatial tracking; this combination places individual behavior in the context of the social and built environment. These efforts have already shown both expected and unexpected relationships between neighborhood surroundings and emotional/behavioral States. These findings can inform scientific theory about addiction and other psychiatric disorders, as well as the implementation and evaluation of public-health policies. NIDA is now focusing on methods that can predict the immediate behavioral future (for example, risk of lapse to drug misuse or HIV-transmitting behaviors) based on input that poses the least possible burden to the user (for example, GPS tracks rather than frequent self-reports). These future-prediction methods could be the basis of treatment interventions that are automatically triggered by and delivered through smartphones, exactly when and where they are needed. NIDA has a patent application submitted for prediction methods. In collaboration with the Biomedical Informatics Section, NIDA also has developed and tested a program to deliver HIV-risk reduction education via smartphone.

WALKABILITY

Question. Dr. Collins I'd like to ask about NIH's research regarding the physical and mental health impacts of walkable, livable communities. Last fall a researcher presented the results of a study funded by the National Institute on Aging, administered through the University of Kansas Alzheimer's Disease Center that suggests towns designed to promote walking can actually blunt cognitive decline in older adults. In addition to mental health benefits it has been suggested that cities planned to be "age-friendly" can reduce pedestrian fatalities, increase exercise and increase opportunities for socialization and community involvement across all age groups. Can you provide a summary of NIH's body of research on the impact of a person's built environment on his or her mental and/or physical health? Can you provide an update about any ongoing studies NIH is funding or participating in regarding the impact of a person's built environment on his or her mental and/or physical health? Earlier this year the Washington Post reported on a trend by physicians to prescribe physical activity to combat certain mental and physical ailments. Has the NIH studied the efficacy of this type of treatment compared to prescription drug interventions?

Answer. Research on the effect of the "built environment"—the physical environment in which humans function—on health and well-being has long been of interest to several NIH Institutes and Centers. For example, in 2004, the National Institute of Environmental Health Sciences (NIEHS) hosted the "Obesity & the Built Environment: Improving Public Health Through Community Design" conference that brought together partner researchers, planners, healthcare providers, developers, policy makers, and community and business leaders. More recently, in 2009, NIEHS hosted the third and final meeting of grantees in the Obesity and Built Environment (OBE) Program. A key aim of the meeting was how modifiable aspects of the built environment can influence overweight and obesity among residents and how those factors may be manipulated to improve public health.

Some NIEHS-supported research has indicated that older individuals who live in neighborhoods with more "walkability" experience a slower rate of decline in leg strength. Small park areas in neighborhoods seem to increase physical activity of families with children, and children who live in neighborhoods with more trees are generally more physically active.

The National Institute on Aging supports a number of studies on aging and the built environment, with studies on how physical surroundings influence mobility,

health, and wellbeing. The Eunice Kennedy Shriver National Institute on Child Health and Human Development has supported research on potential associations between aspects of the built environment and childhood obesity, and the National Heart, Lung, and Blood Institute supports studies on the influence of the physical environment on exercise behaviors, health, and function.

A few of the many currently active studies in this area include:

—A study investigating the relationship between physical exercise and depression risk in older adults, as well as the influence of the neighborhood environment on both of these factors. The research team is also evaluating the impact of a program to improve pedestrian safety for older adults that will be implemented in 10 neighborhoods within the study area over the course of the project (R01 MH085132–05).

—A study examining the relationships between neighborhoods built environment, use of physician services, and preventable hospitalizations and emergency department visits among elderly, chronically ill Medicare beneficiaries in an urban environment (K01 AG039463–05).

—A project to link data on neighborhood characteristics with longitudinal data on cognitive function assessed in a nationally representative sample of older adults in the Health and Retirement Study This study will also examine potential mediators of this relationship, as well as factors that may inform pathways by which neighborhoods influence cognitive outcomes, and will identify subgroups that are most vulnerable to neighborhood effects based on sociodemographic and genetic characteristics (R01 AG043960–03).

—A study drawing on data from the Multi-Ethnic Study of Atherosclerosis and the Study of Women's Health Across the Nation to improve knowledge about physical and cognitive functioning and their decline over time in the context of the neighborhood environment, with special emphasis on social and physical aspects of neighborhoods, and to elucidate how neighborhood environments contribute to race/ethnic and socioeconomic status disparities in function (K01 AG039554–05).

—Studies funded under the Transdisciplinary Research on Energetics and Cancer initiative that investigate mechanisms by which built environment features and policies impact physical activity and obesity and influence carcinogenesis across the lifespan (U54 CA155626, U54 CA155435, U54 CA155850, U54 CA155496, U01 CA116850).

—The Healthy Communities Study, a national study of community-based initiates, environment characteristics, and family and child factors that influence childhood diet, weight, and physical activity (BAA NHLBI–HB–10–15).

—Studies of the effects of mass transit availability, including bus and light rail, on physical activity and health outcomes (Several from NCI and NIDDK)

NIH has studied physical activity and exercise to prevent and treat a variety of diseases and conditions. One prominent example is the Diabetes Prevention Program, which found that both lifestyle changes (diet and exercise) and treatment with the drug metformin reduced the incidence of diabetes in persons at high risk; however, the lifestyle intervention was more effective than metformin—particularly among study participants over age 60. At the 10 year follow-up, the investigators found that incidences in the former placebo and metformin groups fell to equal those in the former lifestyle group, but the cumulative incidence of diabetes remained lowest in the lifestyle group. Prevention or delay of diabetes with lifestyle intervention or metformin can persist for at least 10 years.

Other studies comparing physical activity or exercise to prescription drug interventions include:

—The MS FLASH (Menopause Strategies: Finding Lasting Answers for Symptoms and Health) suite of studies tested promising treatments, mostly non-hormonal, for the most common symptoms of menopause (e.g., hot flashes and night sweats). Investigators found that yoga did not improve hot flash frequency or severity; however, participants reported an improvement in quality of life.

—An ongoing study is comparing changes in bone strength at the hip and spine in women who take 12 months of either: 1) optimal calcium and vitamin D alone; 2) bisphosphonate risedronate with calcium and vitamin D; or 3) a bone-loading exercise program with calcium and vitamin D.

In addition, exercise is being studied as an adjunct to standard treatment for a number of conditions, including cognitive decline and Alzheimer's disease, cardiovascular disease, osteoporosis, and arthritis.

QUESTIONS SUBMITTED TO DR. DOUGLAS LOWY

QUESTIONS SUBMITTED BY SENATOR JERRY MORAN

NCI DESIGNATED CANCER CENTERS

Question. As many people know, those of us in Kansas are very proud of the research conducted at the University of Kansas and felt a sense of pride when the KU Cancer Center was recognized as a "National Cancer Institute-Designated Cancer Center" in June 2012. I understand that many NCI-Designated Cancer Centers, including KU, have community partners to help expand their reach and to ensure that a broader population has access to clinical research. Can you explain how that model works, and if this is a standard approach of NCI-designated cancer centers?

Answer. NCI and NIH share your commitment to ensuring cancer patients have access to NCI-supported clinical trials. Earlier this year, NCI's-designated Cancer Centers Program added its 69th institution, and four other centers were awarded the comprehensive designation. Much of the work these centers do is collaborative, often with researchers at other NCI-designated cancer centers as well as with smaller hospitals and community clinics.

NCI-designated cancer centers and many community hospitals around the country are part of the network of institutions that comprise NCI's two major clinical research programs: the National Clinical Trials Network (NCTN) and the NCI Community Oncology Research Program (NCORP). NCTN and NCORP form a network of 2,400 clinical sites that covers most of the United States, ensuring that patients, regardless of where they live, have access to trials that are testing the latest in cancer prevention, early detection, treatment, and survivorship care.

The overall goal of NCORP is to bring cancer clinical trials and cancer care delivery research to individuals in their own communities, and to contribute to improved patient outcomes and a reduction in cancer disparities. NCI supports 53 NCORP sites across the country, including two sites in Kansas—the Wichita NCORP and the Kansas City NCORP. These 53 community sites and research bases extend their reach even further through a network of 840 component sites—local cancer centers, hospitals, and clinics that are affiliated with the NCORP network and make NCI-supported clinical trials available in a community setting. For example, in Kansas, the Wichita and Kansas City NCORPs include 24 component sites across the State.

NCTN was designed to respond rapidly to new and emerging scientific opportunities. Foremost among these opportunities are precision medicine clinical trials—a new generation of clinical studies focused on developing molecularly targeted and immune-based therapies. The majority of NCTN's lead sites are located within NCI-designated cancer centers, and many NCORP sites collaborate with NCI-designated cancer centers through their participation in NCTN. NCORP facilitates patient and provider access to treatment and imaging trials from the NCTN, and contributed substantially to patient accrual to NCTN trials. For example, 240 affiliates of 13 NCORP sites accounted for seventy percent of all sites preregistered to the NCI Molecular Analysis for Therapy Choice (MATCH) precision medicine trial launched in August 2015.

Additionally, NCI supports the Partnerships to Advance Cancer Health Equity (PACHE) program, which enables NCI-designated cancer centers and institutions serving health disparity populations and underrepresented students to conduct research in cancer and cancer health disparities, train scientists from diverse backgrounds, and effectively deliver cancer advances to underserved communities. NCI currently funds twenty PACHE partnerships.

The NCI-designated Cancer Centers Program, NCTN, and NCORP form the foundation of NCI's clinical research efforts and are critical in brining NCI-supported clinical trials to patients in their own communities. The continued growth of the Cancer Centers Program, and the partnerships it fosters, is essential to the success of the National Cancer Program.

NCI PRECISION MEDICINE

Question. Dr. Lowy, what do you envision for how the NCI will facilitate the NIH's precision medicine initiative? Is there potential for supplemental Cancer Center Support Grant awards to implement precision medicine initiatives like the MATCH trial?

Answer. Cancer presents an exceptionally promising opportunity to refine the principles and practices that will serve as the foundation for precision medicine. The additional funding associated with the precision medicine initiative (PMI) will allow NCI to expand the NCI–MATCH study. This expansion will include the addition of new genetically targeted therapies to which patients can be matched and an in-

crease in the number of genetic alterations included in the study. MATCH is implemented through the NCI Clinical Trials Network (NCTN), a group that is formally connected to many NCI-designated cancer centers by their designation as "lead academic participating sites" or "LAPS" sites. All NCI-designated cancer centers and all NCI's Community Oncology Research Program (NCORP) sites can enroll patients into the MATCH study. PMI funding will also accelerate planning for the Pediatric MATCH study. NCI will continue to provide details and updates to the committee on established NCI programs in precision oncology and the status of NCI progress related to the new and expanded activities under the fiscal year 2016 Precision Medicine Initiative.

The 69 NCI-Designated Cancer Centers form the backbone of NCI's programs for studying and controlling cancer, and they will be critically involved in precision medicine initiatives at every stage of the research continuum. NCI's PMI efforts will be focused on further developing and expanding research in the following areas:

—Evolution of a new standard for clinical trials in which the molecular characterization of cancers becomes the clinical standard for accurate diagnosis and treatment. This requires identifying or developing an array of treatments that can be matched to the molecular features of a tumor to successfully control the disease, overcoming drug resistance in cancer treatment. The goal is to develop cancer models from tissues obtained at the time of diagnosis and at relapse to uncover mechanisms of resistance to treatment. This involves analyzing tumor DNA and tumor cells circulating in blood samples to develop methods to predict relapse before this problem is identified clinically or in radiologic studies. It also includes testing combinations of targeted agents in clinical trials.

—Development of new laboratory models for research by greatly increasing the number of human cancer cell lines available, as well as the number of patient-derived tumor xenografts—model systems developed by transplanting a patient's tumor cells into laboratory mice. Providing these and other tools to researchers to gain new insights into tumor biology and better predict patients' responses to cancer treatment.

—Development of a national cancer knowledge system to support precision medicine by building an information platform. This would support the integration of genetic information about tumors with data on how the tumors respond to therapy, and incorporate genetic, biochemical, environmental and clinical data from patients to define molecular subtypes and to identify the approaches to cancer care that will improve patient outcomes.

NCI will work to achieve these goals by using its existing infrastructure such as the NCI-Designated Cancer Centers, the NCTN, and the NCORP, which supports consortia of community hospitals, oncology practices, and integrated healthcare systems across the country. This program includes a specific focus on underserved populations, with twelve NCORP Minority/Underserved Community Sites with patient populations comprised of at least thirty percent racial/ethnic minorities or rural residents. NCI also supports a partnership program between NCI-designated cancer centers and institutions serving underserved health disparity populations that aims to train scientists from diverse backgrounds in cancer research and to effectively deliver cancer advances to underserved communities.

QUESTIONS SUBMITTED BY SENATOR MARK KIRK

STOMACH CANCER IN YOUNG PEOPLE

Question. I am gravely concerned about the rise of stomach cancer in young people. This recalcitrant cancer hides until it is late stage and is deadly when metastatic; only 4 percent survive when diagnosed at late stage. The research investment for this cancer is severely lacking and the science is not as advanced as it is for other cancers. I hear from stomach cancer researchers that it is very difficult for them to get funded in the competitive grants environment and that the lack of funding is deterring investors from the field of stomach cancer research altogether.

It is my understanding that promising stomach cancer data is available from The Cancer Genome Atlas (TCGA). What is the NCI doing to translate TCGA-generated knowledge to actual advances for stomach cancer patients, for whom there is a lack of effective treatments? While I understand the promise of the NCI MATCH Trial, researchers tell me it will have limited utility for stomach cancer.

Answer. NCI is committed to full exploration of the data from The Cancer Genome Atlas (TCGA) and similar projects to advance genomic research and translate findings into the clinic to improve the precise diagnosis and treatment of cancers such as gastric cancer. NCI supports a wide range of basic research projects and

clinical trials on gastric cancer, including five Specialized Programs of Research Excellence (SPORES) focused on gastrointestinal cancers such as stomach, esophagus, and colon cancers. NCI is currently sponsoring several clinical trials for gastric and gastro-esophageal (GE) cancers. Examples include a study of combination chemotherapy for gastric cancer, a study of a targeted therapy with personalized antibodies for GE cancer, and a phase II study of a drug that inhibits tumor growth receptors for advanced esophageal gastric cancer. In addition, NCI's National Clinical Trials Network (NCTN) is currently supporting several trials for gastric cancer, including a trial of combination therapy for gastric cancers with high hepatocyte growth factor receptor (HGFR) expression, as well evaluating whether the addition of molecularly-targeted therapies can enhance the survival of patients treated with combinations of traditional surgical, radiation, and chemotherapeutic approaches. It is too early to tell what the NCI MATCH Trial will yield for any particular cancer type, and there are several applicable targets for gastric cancer, including human epidermal growth factor receptor 2 (HER2), epidermal growth factor receptor (EGFR), and Epstein-Barr virus (EBV).

Sequencing data from TCGA has enabled the extensive characterization of cancer genomes as well as associated analyses across cancer types that have shown that some cancer subtypes may be more similar to each other than to others from the same organ-of-origin. These analyses (called Pan-Can analyses) have also shown that these cancer types also might share common genetic features that could be susceptible to some targeted therapies on the market, but not yet considered for the particular subtype. In other words, seemingly dissimilar cancer types may share a vulnerability for which a drug is already available. NCI is supporting new projects to expand on these analyses and to enable researchers to examine a variety of new research hypotheses in this area.

NCI is also supporting the development of new cancer models, including gastric cancer models, sometimes referred to as "organoid" cultures and "conditionally reprogrammed" cells. NCI has completed a pilot program in the development of these organoid models and is co-leading an international consortium effort for broad development of models for many cancer types. When successful, NCI will distribute these new cancer models broadly to cancer researchers to help develop diagnostic and treatment strategies tailored to specific subtypes of cancer and to specific molecular abnormalities.

Question. Additionally, if stomach cancer researchers have difficulty competing for research grants because the knowledge base of stomach cancer is lacking, what can NCI do to help level the playing field?

Answer. NCI's investment in TCGA and a pilot study specifically to obtain biospecimens for gastric cancer has enabled more successful applications focused on gastric cancer research. The success rate for all gastric cancer grant applications (both new and competing) ranged from 16 percent and 46 percent between fiscal years 2010–2014, with the highest gastric cancer success rate to date was in fiscal year 2014, with 46 percent of gastric cancer applications being funded. The average success rate for all NCI grant applications during this time period ranged 12–14 percent.

Results from TCGA analyses to date have led to more than 3,000 articles in research journals. Data from TCGA has not only generated a large number of publications, it has also stimulated many new research proposals, many of which have been funded. To date, NIH has received over 3,000 grant applications utilizing TCGA data, and the success rate for these applications has been above the NIH average. NCI will continue to support promising research proposals that address important scientific questions, and will use the breadth of funding mechanisms available to support both individual and team science approaches. Projects like TCGA are providing a new classification framework focused on the genetic abnormalities of cancer that has the potential to alter diagnostic categories, enhance treatment strategies, enable early detection and prevention, and improve outcomes for all patients. NCI is seeking innovative research proposals to advance these goals through a variety of funding opportunity announcements.[8]

Question. Researchers and patients alike tell me a dedicated funding stream, such as a through a RFA for stomach cancer, would help to bridge the research gap and give hope to the many young people who have or will be diagnosed with stomach cancer. Is this something NCI could consider to assist these patients?

Answer. NCI is fostering many opportunities to study gastric (stomach) cancer via several different types of funding opportunity announcements (FOAs) supporting a wide variety of investigator-initiated research applications ranging from basic studies of cancer etiology and structural biology to studies of early detection and bio-

[8] Http://deais.nci.nih.gov/foastatus/RFA-PA.jsp.

markers and clinical trials. An "RFA" (request for applications) is a specific funding mechanism with set-aside funds that is typically utilized for defined research areas, and one that may be appropriate in the future for specific gastric cancer research projects. NCI is also supporting training opportunities for talented individuals who might develop an interest in gastric cancer through individual fellowships, institutional training awards, and career development awards; and NCI program managers are available to provide guidance to investigators who seek help in finding the most appropriate funding mechanisms to support proposed work on gastric cancer and other types of cancers.

QUESTION SUBMITTED BY SENATOR JACK REED

CHILDHOOD CANCER

Question. Director Douglas Lowy, National Cancer Institute—Childhood Cancer: In July, I introduced the Childhood Cancer Survivorship, Treatment, Access, and Research (STAR) Act, along with my colleague on the Subcommittee, Senator Capito. The legislation would expand opportunities for childhood cancer research, improve efforts to identify and track childhood cancer incidences, and enhance the quality of life for childhood cancer survivors. As you know, cancer remains the leading cause of death by disease among our children—and while research supported by NIH and NCI is leading to progress, we still have a long way to go. What do you see as the most promising research opportunities in this area, and what is NCI doing to support these efforts?

Answer. NCI is committed to advancing research on all fronts to benefit children with cancer—from basic science to preclinical studies, translational research, and clinical trials, as well as efforts focused on survivorship, quality of life, and psychosocial care. This work is represented by key investments across our extramural portfolio, at cancer centers and institutions across the country, as well as through NCI's Pediatric Oncology Branch at the NIH Clinical Center.

These priorities include a new 5-year commitment to NCI's Pediatric Preclinical Testing Consortium and significant investments in NCI's Children's Oncology Group to support pediatric clinical trials, including the NCI Pediatric Molecular Analysis for Therapy Choice (Pediatric MATCH) trial. Pediatric MATCH will provide a tremendous opportunity to test a range of molecularly targeted therapies in children with advanced cancers who have few other treatment options. With the genomic data captured in the trial, it will also produce an invaluable resource for studying the genetic basis of relapse in pediatric cancers. Through the Children's Oncology Group, NCI is also supporting nationwide clinical trials introducing new immunotherapy agents into evaluation for children with cancer and clinical trials evaluating precision medicine concepts in children with newly diagnosed lymphomas and leukemias.

In addition to these efforts, NCI has prioritized the development of new treatments for pediatric cancer in the NCI Experimental Therapeutics (NExT) Program.[9] This program focuses on advancing breakthrough discoveries in basic and clinical research into new therapies, and several new inhibitors with potential to treat pediatric cancer are being studied for this purpose.

NCI's translational research efforts include a recently awarded a Specialized Program of Research Excellence (SPORE) award focusing on neurofibromatosis type 1 and related cancers in children and adolescents and young adults. This award is exciting for a number of reasons. This is the first SPORE grant that is non-organ specific, and instead targets a pathway—known as the RAS pathway. SPORE grants are also typically awarded to a single institution, and this effort is collaboration across institutions—including the University of California San Francisco, Indiana University, the University of Alabama, and the Johns Hopkins University. The effort will also include a focus on cancer survivorship and understanding how chemotherapy and radiation promote the development of second cancers—a critical issue for pediatric and adult cancer survivors.

Childhood cancer survivorship research continues to be a priority for NCI. The Childhood Cancer Survivor Study, launched by NCI more than two decades ago, is a critical resource for investigators conducting survivorship research, as well as for clinicians making treatment decisions and delivering survivorship care. NCI also supports a complementary effort, the St. Jude Lifetime study, which will allow for replication of findings from genomic studies and the development of collaborative

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[9] Http://next.cancer.gov/about/mission.htm.

projects to refine risk-based follow-up guidelines and improve outcomes among childhood cancer survivors.

NCI continues to support new research opportunities and collaborations in pediatric oncology. In February 2015, NCI brought together dozens of experts to identify critical gaps in our knowledge about the genetic changes underlying childhood cancers.[10] The Childhood Cancer Genomics Gaps and Opportunities workshop included researchers and clinicians, members of regulatory agencies, and advocates for research on childhood cancers. A full summary of the workshop is available on NCI's website.[11] Participants continue to collaborate to pursue opportunities identified at the workshop, and the workshop discussions also informed NCI's decision to support Provocative Questions (PQ) meetings focused specifically on pediatric cancers.[12] NCI's PQ initiative aims to promote cancer research on important yet understudied areas or research questions that have proven difficult to address. NCI launched the PQ effort in 2011 to build on specific advances in cancer biology and cancer control, and to address critical questions about cancer biology that were largely unresolved. The questions are generated from the cancer research community through NCI-sponsored interactive workshops with researchers. Two of the most recent PQ workshops took place in November 2015 and focused exclusively on identifying questions to advance pediatric oncology research.

We agree that the current outlook for children with cancer and their families is not acceptable—and NCI is committed to doing more to identify promising new therapies for children, bring these therapies to the clinic, improve the outlook for childhood cancer survivors, and support the foundation of basic research needed to achieve all of these goals.

QUESTION SUBMITTED TO DR. GRIFFIN P. RODGERS

QUESTION SUBMITTED BY SENATOR ROY BLUNT

KIDNEY DISEASE

Question. Dr. Rodgers, Medicare provides care for every American with kidney failure, regardless of age. This is an incredibly expensive endeavor and a good example of how research could slow the progression of the disease or help develop more cost-effective treatments for those with kidney disease. Research would have both huge health benefits and cost savings for the U.S. taxpayer. Could you update the Committee on your Institute's latest efforts in kidney research?

Answer. Yes, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) is vigorously supporting research to identify causes of kidney diseases, slow or stop disease progression, develop treatments, and prevent kidney diseases and kidney failure in adults and children. For example, results from the Chronic Renal Insufficiency Cohort Study, which is evaluating long-term cardiovascular risk and outcomes of over 3,700 persons with chronic kidney disease (CKD), showed that systolic blood pressure levels above 130 mmHg -below the current guideline threshold of 140 mmHg—is associated with worse kidney outcomes. Building on the importance of blood pressure control, the NHLBI-led and NIDDK-supported Systolic Blood Pressure Intervention Trial (SPRINT) is examining the effects of intensive blood pressure control on the development of kidney disease, and results are expected to be reported in November 2015.

NIDDK is also studying children with mild to moderately decreased kidney function in the Chronic Kidney Disease in Children (CKiD) study. The study is examining risk factors for further kidney decline, as well as investigating risk factors for heart disease, closely monitoring brain development, and following long-term effects of poor growth in this group. The study has already found that growth is relatively stunted in lower-income youth with kidney disease. In a related effort, NIDDK is supporting the planning phase of a trial of phosphate binders to treat children with bone disease as a result of their CKD.

NIDDK established and is recruiting participants for the CKD Pilot Trials Consortium to help advance possible new CKD therapies. A current clinical trial is testing whether the generic drug allopurinol could preserve kidney function in people with type 1 diabetes who are at high risk of kidney disease; if the result is positive, it could represent a low cost approach to prevent kidney disease in this population and potentially in people with type 2 diabetes. NIDDK also renewed a consortium

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[10] Http://www.cancer.gov/news-events/cancer-currents-blog/2015/childhood-genomic-workshop.

[11] Http://www.cancer.gov/types/childhood-cancers/research/childhood-genomics-workshop-summary.pdf.

[12] Http://provocativequestions.nci.nih.gov/.

to promote the discovery and validation of CKD biomarkers. Biomarkers could allow earlier detection of disease and thus facilitate earlier treatment, and also enable clinicians and researchers to measure responses to therapy.

An ongoing effort related to kidney dialysis is a large, pragmatic clinical trial comparing the effect of adding 30 minutes to the usual (3.5 hour) duration of dialysis treatments for new dialysis patients. The trial will determine if the extra dialysis time increases survival, reduces hospitalizations, and improves health-related quality of life. NIDDK also is leading Improving Chronic Disease Management with Pieces (ICD-Pieces), which is a trial in four large healthcare systems that is testing a novel health information technology (HIT) approach to reduce hospitalizations in people with CKD, hypertension, and diabetes.

To increase knowledge about nephrotic syndrome, a kidney disorder that can be caused by a number of diseases, NIDDK recently expanded the Nephrotic Syndrome Study Network (NEPTUNE) observational study, which now includes a specific pediatric component. NEPTUNE is investigating the underlying causes of nephrotic syndrome, toward identifying new therapeutic targets. Complementing NEPTUNE, the new Cure Glomerulopathy Network consortium will conduct translational and clinical research to better understand the causes, treatments, and progression of several forms of kidney disease. The Network is recruiting 2,400 patients, of which at least 25 percent will be children. NIDDK also supports the Assessment, Serial Evaluation, and Subsequent Sequelae of Acute Kidney Injury (ASSESS–AKI) study, which will provide important information about the natural history of AKI and recovery.

Recent findings from major NIH trials and studies are providing novel insights about genetic contributions to the increased risk of non-diabetic kidney disease in African Americans. For example, researchers in the SPRINT study found that variants in the APOL1 gene are associated with increased risk of kidney disease, but not cardiovascular disease, in African American participants with high blood pressure. Additionally, results of a study leveraging five NIH-supported cohort studies suggest that sickle cell trait may be related to the higher risk of kidney disease in African Americans. These insights can help identify ways to reduce the burden that kidney disease places on this population.

To inform future directions for kidney disease research, the NIDDK spearheaded a Kidney Research National Dialogue, engaging kidney disease researchers in a discussion to identify research strategies that would improve understanding of normal kidney function and the mechanisms underlying kidney disease. The ideas that arose from these discussions were distilled and published in a series of commentaries—making them available to the broader community interested in kidney disease research. Complementing that effort, the Institute has also sponsored several recent scientific conferences and workshops that are informing future research directions related to kidney diseases. Topics of recent meetings included overcoming barriers in AKI, APOL1 and kidney disease, urinary stones, and the use of health information technology to identify and manage CKD populations.

QUESTIONS SUBMITTED BY SENATOR PATTY MURRAY

DIABETES PREVENTION RESEARCH

Question. NIDDK strongly supported the development and testing of the Diabetes Prevention Program. The Diabetes Prevention Program helps overweight participants with pre-diabetes to become physically active and lose weight. In multiple trials, participants have become more active, lost weight, and reduced the onset of diabetes in at-risk populations by about 60 percent. The YMCA estimates that 30 percent of adults could benefit from participation in the Diabetes Prevention Program, yet real-world participation is disappointingly low. What kind of research is NIDDK conducting to learn how to increase participation in the program?

Answer. The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) is pursuing several areas of research that could help increase participation in the National Diabetes Prevention Program (NDPP). NDPP is a public health program led by the Centers for Disease Control and Prevention (CDC) that is based on NIDDK-supported research: the original NIDDK-led Diabetes Prevention Program (DPP) clinical trial, as well as a subsequent NIDDK-supported pilot study showing that local Ys could be used to deliver a lower-cost, group-based adaptation of the DPP lifestyle intervention. CDC launched the NDPP based on results of the pilot study, but it was important to have a larger and longer-term study to provide more definitive evidence for delivery through local Ys. NIDDK funded that recently published study, which showed that using the Ys to deliver the DPP lifestyle intervention achieved meaningful weight loss at 12 months in low-income adults.

Through its Centers for Diabetes Translation Research program, NIDDK also supported research showing that implementation of a group-based DPP lifestyle program adapted for American Indian/Alaska Native communities—populations disproportionately affected by type 2 diabetes—prevented or delayed onset of the disease. This study demonstrated the feasibility of using a DPP-based lifestyle intervention in these communities, which can inform future public health efforts to recruit and retain participants. Additionally, NIDDK supported a small business grant to Omada Health for online delivery of the DPP lifestyle intervention; the online program is now NDPP-certified (https://preventnow.com/). Having an online option could help reach more people, particularly those who may not live near an in-person program or have schedules that permit in-person participation.

NIDDK also supports behavioral research that could inform efforts toward increasing participation in the NDPP, such as a pilot study specifically seeking to increase NDPP recruitment, group participation, and retention of men from low resource areas, based on observations that NDPP participation rates for men, particularly those from minority populations, are lower than rates for women. NIDDK is also supporting research examining other ways to deliver the DPP lifestyle intervention in a variety of community settings to high-risk or underserved populations through more efficient and scalable means. For example, one research effort is testing a group-based DPP lifestyle intervention delivered by community health workers at community centers, and another is examining the approach of offering a DPP-based lifestyle program to at-risk retirees during the annual Medicare enrollment process. These and other efforts can test novel, low-cost, and scalable ways to reach greater numbers of people who are at risk for type 2 diabetes and enroll them in DPP-based lifestyle programs.

Screening to identify people with prediabetes who could benefit from the NDDP is an important component to increasing participation in the Program. The same simple blood tests identify people with prediabetes or undiagnosed diabetes; in the United States, there are an estimated 86 million adults with prediabetes and 8.1 million people with undiagnosed diabetes. In 2013, NIDDK scientists published a study showing that following the U.S. Preventative Services Task Force's (USPSTF's) recommendations for diabetes screening—to recommend screening only for individuals with high blood pressure—missed about half of the people with undiagnosed diabetes in the U.S. I am pleased to report that the USPSTF recently updated its screening guidelines to recommend that doctors screen for diabetes and prediabetes in all of their adult patients ages 40 to 70 who are overweight or obese. Because this is a "B grade" recommendation, screening for eligible individuals will be covered under the Affordable Care Act. This expanded screening could help identify more people who have prediabetes and thus could benefit from enrolling in NDPP.

Finally, NIDDK continues to follow the original DPP cohort in the DPP Outcomes Study (DPPOS) to determine long-term outcomes and durability of the DPP interventions. DPPOS has found that the lifestyle intervention continues to be effective for at least 10 years, and that it is especially effective in people over age 60 and is highly cost effective. Additionally, the study is examining intervention effects on other health-related outcomes, including co-morbid conditions such as depression.

Question. How is NIDDK working with other agencies like the CDC and HRSA to increase use of the program?

Answer. NIDDK works closely with CDC on the jointly sponsored National Diabetes Education Program (NDEP). NDEP works with over 200 public and private partners at the Federal, State, and local levels to improve treatment and outcomes for people with diabetes, promote early diagnosis, and prevent or delay the onset of type 2 diabetes. One way that NDEP works to enhance participation in NDPP is by increasing awareness about the program through its educational materials for people at risk for type 2 diabetes, their families, and their healthcare providers. For example, information about NDPP is available as part of the "Small Steps. Big Rewards" educational campaign that, based on DPP findings, provides tools for people at risk for type 2 diabetes to take steps to reduce their risk of developing the disease. For healthcare providers, information about NDPP is provided in NDEP's Guiding Principles document, which is a resource that helps guide primary care providers and healthcare teams to deliver quality care to adults with or at risk for diabetes. NDPP also is included in NDEP's GAMEPLAN toolkit and website for healthcare professionals. These types of resources can help increase awareness of NDPP, so that people at risk know about the program and that healthcare providers could refer their patients to it.

Additionally, NIDDK collaborates with other Federal agencies, including CDC, the Centers for Medicare & Medicaid Services (CMS), the Indian Health Service (IHS), the Heath Resources and Services Administration (HRSA), and the Veterans Health

Administration (VHA) on the statutory Diabetes Mellitus Interagency Coordinating Committee (DMICC), which NIDDK chairs. DMICC facilitates cooperation, communication, and collaboration on diabetes among government entities. NDPP was announced at the November 10, 2009 DMICC meeting, where initial results of the Y-based DPP adaptation were also presented, and the Committee expects to follow up on the NDPP in the near future. DMICC meetings also serve as important venues to share information. For example, results of the DPP itself and of the research that I described in response to your first question were shared at DMICC meetings, which could help inform public health and health delivery efforts by CDC, CMS, IHS, HRSA, and VHA. Additionally, IHS and VHA efforts to implement the DPP lifestyle intervention for the populations they serve have been discussed at DMICC meetings.

QUESTIONS SUBMITTED TO DR. WALTER J. KOROSHETZ

QUESTIONS SUBMITTED BY SENATOR ROY BLUNT

DEPARTMENT OF DEFENSE BRAIN BANK

Question. The Department of Defense and the NIH are partnering to create the world's first human brain tissue repository for military personnel. However, it is my understanding that NIH researchers are having issues accessing post-mortem tissues from service members affected by blast injury. Dr. Koroshetz, can you discuss the importance of having access to brains that have experienced blast injuries?

Answer. We do not know in what ways blasts have similar and different effects on the brain compared to impact injuries, or rapid acceleration/deceleration injuries. The behavioral effects of blast TBI may appear similar to other TBI, but examining brain tissue is key to understanding both whether blast injury causes distinct pathology in the brain, and how to prevent it in the future. Although Department of Defense laboratories are studying the effects of blast injuries on animals, and scientists are also using computer models to try to model the physical effects on the brain, it is essential to also study human brains to understand the effects of blast injury, both in the short and long term. The human brain is unique in many ways, and the much larger size of the human brain, especially the cerebral cortex, compared to animals can substantially change the physical forces on brain tissue from blast injury. The lack of a systematic evaluation of blast injury in human brain is a major barrier to advancing research for those servicemen and women who have experienced blast injury in the past or may experience it in the future.

Question. What are the hurdles you are facing to gain access to these resources?

Answer. An April 2015 Report to Congress entitled "Overcoming the Challenges of Obtaining Postmortem Brain Specimens from U.S. Service Members" addresses research on brain samples and release of information without a change of DOD policy for consent or interaction with families of deceased service members. The solutions outlined in this Report to Congress were considered the most appropriate and expedient ways to enable brain tissue donations. A neuropathology laboratory has been set up for the purpose of defining the pathology of blast injury through the joint

Uniformed Services University of the Health Sciences."-NIH Center for Regenerative Medicine (USUHS–CNRM) and the U.S. Army Medical Research and Materiel Command. Brain tissue in the USUHS–CNRM brain tissue repository can be accessed by investigators at any institution that has appropriate regulatory approval. CNRM has a USUHS Institutional Review Board-approved policy for tissue distribution and a steering committee that oversees the processes. NIH continues to work with DOD to improve processes for obtaining brain tissue samples for research.

ALTERNATING HEMIPLEGIA OF CHILDHOOD

Question. Dr. Koroshetz, Alternating Hemiplegia of Childhood (AHC) is a neurodevelopmental disorder characterized by repeated episodes of weakness or paralysis that may affect one side of the body or the other. It is rare, estimated to occur in approximately 1 in 1,000,000 births. However, since cases may go unrecognized or misdiagnosed, it is difficult to determine the true frequency of AHC in the general population. What research is currently ongoing related to AHC and what are future research plans likely to focus on, specifically?

Answer. This August I gave the keynote address at the "4th Symposium on ATP1A3 in Disease" in Bethesda. Alternating hemiplegia of childhood is one of several diseases caused by mutations in the gene ATP1A3. Others include, for example,

types of dystonia-Parkinsonism and epilepsy. The Bethesda meeting brought together researchers, including those supported by the NIH, and the disease advocacy community to share the latest findings, brainstorm about future directions, discuss collaborations, and highlight funding opportunities.

AHC illustrates how decades of NIH investment can come to bear on a particular rare disease. ATP1A3 mutations affect the sodium-potassium ATPase, or "sodium pump," which maintains the balance of ions that is crucial for electrical activity and other cell functions. This critical pump utilizes 50 percent of the brain's energy supply. Understanding how mutations disrupt function was accelerated by many years of basic studies on the sodium pump, including ongoing research by intramural and extramural NINDS investigators. Researchers have also capitalized on new technologies, such as the recent advances in gene sequencing, to help identify the many different mutations (more than 100), that can alter the function of this ATPase.

NINDS is currently funding research to understand the full range of developmental, motor, cognitive, and psychiatric symptoms that mutations in this gene can cause, which may allow a shared approach to therapy for the various diseases caused by mutations in this gene based on the underlying cause. Researchers are also applying advanced brain imaging to identify the brain areas that are affected. This may enhance future clinical trials and the ongoing care of patients by providing objective measures of progress over time, and could point the way to design of future treatments, including deep brain stimulation. Ongoing studies of how the mutations affect cells at the molecular level of analysis will contribute to the design of rational therapies.

As discussed at the symposium, NINDS provides a wide range of funding opportunities designed to support research across the full spectrum from basic research of disease mechanisms, through laboratory development of potential therapies, through clinical trials. One specific area of focus for future research involves the NeuroNEXT clinical network, which is designed to facilitate early phase clinical trials as potential treatments emerge, especially for rare pediatric disorders. The Institute also works closely with other parts of the NIH, including the Office of Rare Diseases Research to facilitate research on diseases like AHC.

QUESTIONS SUBMITTED TO DR. NORA D. VOLKOW

QUESTIONS SUBMITTED BY SENATOR ROY BLUNT

OPIOID RESEARCH

Question. Dr. Volkow, there has been a significant increase in prescription drug abuse over the last several years. What is NIDA's role in researching new pain medications that may reduce abuse?

Answer. NIDA supports several different areas of research to develop alternative pain treatments with reduced potential for abuse. Pain is a symptom of many health problems and disease states, and pain research is funded by many NIH Institutes and Centers (ICs). The NIH Pain Consortium was established to enhance and facilitate pain research and promote collaboration among researchers addressing pain by coordinating funding opportunities across the 25 participating NIH ICs (including NIDA) that support pain research.

NIDA specifically supports both clinical and preclinical studies to develop alternative pain treatments focused on the development of:

—Medications that target the opioid system in new ways to reduce abuse potential. NIDA is engaging in strategic partnerships with pharmaceutical and biotechnology companies, private and public foundations, and small businesses to identify safer and more effective treatment options. Some examples include:
  —A partnership with Signature Therapeutics to develop an abuse deterrent formulation of OxyContin that uses prodrug technology—attaching an extension to the opioid molecule which renders the drug inactive unless it is taken orally.
  —New compounds that exhibit novel properties as a result of their combined activity at different opioid receptors (mu, delta, and kappa). Compounds with combined activity at the mu and delta receptors, or at all three receptors can induce strong analgesia without producing tolerance or dependence in animal models.
—Medications that target non-opioid neurotransmitter systems, proteins, and signaling cascades including:
  —The cannabinoid system. Research has demonstrated the efficacy of cannabinoid compounds on central and peripheral neuropathic pain. A re-

cently announced funding opportunity will support research to explore the therapeutic potential of the endocannabinoid system, which modulates pain through mechanisms distinct from opioids and may have a lower potential for abuse, as there are little to no mood-altering effects.[13]

—The transient receptor potential vannilloid (TRPV–1), which moves to the neuron's surface as nerve cells respond to pain stimuli. Blocking this TRPV–1 movement to the cell surface may be a potent means of preventing severe pathological pain conditions.

—Resiniferatoxin, a novel compound that targets TRPV–1 channels. It produces robust analgesia in animal models of pain and FDA has approved its testing for terminal cancer pain (drug development was also supported by the National Institute of Dental and Craniofacial Research).

—Other methods of selectively silencing pain fibers, including: 1) molecules that interrupt pain signals in pain-specific nerve cells; and 2) optical stimulation using infrared laser light to inhibit activity in pain neurons (photo-analgesia).

—Fatty acid binding proteins that regulate inflammatory and pain responses.

—G-protein receptor 55, which modulates inflammation and pain in animal models.

—Transient receptor potential action channel A1 (TRPA1), which acts as a signal integrator for sensory nerve cells. The potential of TRPA1 antagonists as peripherally acting analgesics is being explored.

—NaV1.7 sodium channels, which play a crucial role in pain signaling. Their modulation is an attractive mechanism under study to treat chronic pain.

—Combinatorial approaches utilizing both opioid and non-opioid systems.

—A current funding opportunity announcement "Clinical Evaluation of Adjuncts to Opioid Therapies for the Treatment of Chronic Pain" aims to identify novel strategies to reduce the amount of opioids administered to patients with chronic pain through combined delivery with other drugs that provide additive analgesic effects to minimize the dose of opioids needed for pain control.

—Non-pharmacological strategies for the treatment of pain. Numerous non-pharmacological interventions have shown promise for the treatment of pain including:

—Neural stimulation therapies—Several brain, spinal cord and nerve stimulation therapies—including transcranial magnetic stimulation, transcranial direct current stimulation, electrical deep brain stimulation, and stimulation devices for peripheral nerves/tissues—have shown promise for the treatment of chronic pain.

—Stem cell therapy—Researchers are exploring the effects of stem cell transplants to generate new pain signaling neurons to reduce inflammation and inhibit chronic pain.

—Gene therapy and epigenetics- New technologies using innovative methods to alter gene expression are providing new targets for therapeutic development.

—Complementary, integrative health approaches—Treatment approaches that consider the biopsychosocial nature of pain, include clinical studies on cognitive behavior therapy, exercise, complementary therapies, and mindfulness practices.

Question. Are there factors that predispose or, conversely, protect against opioid abuse and addiction?

Answer. Although opioid medications effectively treat acute pain and help relieve chronic pain for some patients, their addiction risk presents a dilemma for healthcare providers who seek to relieve suffering while preventing drug abuse and addiction. Little is yet known about the risk for addiction among those being treated for chronic pain or about how basic pain mechanisms interact with prescription opioids to influence addiction potential. To better understand this, NIDA launched a research initiative on "Prescription Opioid Use and Abuse in the Treatment of Pain." This initiative encourages a multidisciplinary approach using both human and animal studies to examine factors that predispose or protect against opioid abuse and addiction.

Several genetic variations have been identified that interact with the way an individual processes and responds to opioid drugs. These include variations in the μ opioid receptor-1 gene (OPRM1) and the enzyme cytochrome P450 2D6 (CYP2D6). Other genetic factors have been linked to differences in pain perception and in response to opioid analgesics. An approach to pain treatment that seeks to integrate these genetic findings is "pharmacokinomics," in which pharmacogenetic (genetic differences in the response to drugs) and pharmacokinetic (how the body processes a drug) information is combined to optimize opioid dosing to minimize addiction

[13] Http://grants.nih.gov/grants/guide/pa-files/PA-15-188.html.

risk. These methods are still in the developmental phase, but offer the potential to personalize pain medicine with an eye toward addiction prevention.

Question. Why are there not more medications available for addiction treatment?

Answer. There are currently three medications approved by the FDA to treat opioid addiction and no FDA approved medications to treat cocaine, methamphetamine, or cannabis use disorders. Developing new and improved treatment options for opioid use disorders remains a high priority for NIDA due to the scope of the current opioid overdose epidemic. Many larger pharmaceutical companies have not entered the addiction market. Some of the possible reasons for this include: the perception of a small market size, the difficulties in executing clinical trials in patients with multiple comorbidities—many injection drug users are HIV or HCV positive and are taking multiple antiretroviral drugs—and the high bar for obtaining approval for addiction medications (the current FDA policy is to ask for a clinical trial endpoint of either abstinence or a pattern of reduced drug use demonstrated to be a valid surrogate for clinical benefit. However, there is not yet sufficient research demonstrating that reduced drug use is a valid surrogate to support use of this alternative end point for FDA approval. NIDA is engaging in strategic partnerships with pharmaceutical and biotechnology companies, private and public foundations, small businesses, and other Federal agencies to address these challenges. For example, NIDA, together with the FDA, academic and industrial partners, are working towards establishing endpoints "other than abstinence" (OTA). One possible alternative measure is "reduced drug use"; however, additional evidence that a reduction in drug use is linked to improved patient outcomes will be required by the FDA to support its use. To this end, in 2013, NIDA issued an RFA entitled: "Identifying Health Outcomes Associated with changes in use of Illicit Drugs" and this year a new program announcement was published on this topic. Results so far include a recent publication which found that reduced use of cocaine, as well as abstinence, decreased endothelial dysfunction—a marker of heart disease risk—characteristic of chronic cocaine use.

Despite these challenges, promising treatments are in development. Some of the most promising findings from basic and clinical research aimed at developing new treatments for opioid addiction include:

—Lofexidine—NIDA has awarded a series of grants to support the development of lofexidine as an adjunctive treatment for use in opioid detoxification. It is anticipated that an NDA for this drug will be filed with the FDA within the year.

—Opioid vaccines—NIDA supports the development of vaccines to treat opioid addiction and prevent relapse. Multiple studies have reported encouraging preclinical results with anti-opioid vaccines. Additional development in this area is ongoing.

—Buprenorphine implants—NIDA supported a Phase III clinical trial of buprenorphine implants, a novel formulation that provides stable round the clock dosing for 6 months. Based in part on this NIDA supported study, a New Drug Application (NDA) was submitted to the FDA. The sponsor (Braeburn Pharmaceuticals) recently performed additional studies requested by FDA with positive results, and a revised NDA was filed in September 2015.

Question. Why is it so difficult to treat?

Answer. Opioid addiction is a complex brain disorder that is influenced by many interacting factors including individual genetics, as well as social, behavioral, and environmental factors. While our understanding of the brain circuits involved in addiction is rapidly increasing, the development of medications that treat brain disorders is notoriously difficult. This is because it is often difficult to get enough of a medication across the blood brain barrier and into the brain without causing toxic effects in the rest of the body. As a result, many promising treatment strategies fail during human clinical trials. However, new tools are being developed to help predict which medications will fail due to human toxicity or failure to cross the blood brain barrier.[14,15] In addition, new technologies to more directly modulate brain circuits—such as transcranial magnetic and deep brain stimulation hold promise for new treatment strategies.

It is also important to note that when prescribed and administered properly, Medication Assisted Treatments (treatment with methadone, buprenorphine, or naltrexone in combination with psychosocial treatment) have proved effective in helping patients recover from opioid use disorders. They are safe, cost-effective, and

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[14] Kamimura H, Ito S. Assessment of chimeric mice with humanized livers in new drug development: generation of pharmacokinetics, metabolism and toxicity data for selecting the final candidate compound. Xenobiotica. 2015 Oct 7:1–13

[15] Griep LM et al. BBB on chip: microfluidic platform to mechanically and biochemically modulate blood-brain barrier function. Biomed Microdevices. 2013 Feb;15(1):145–50.

reduce the risk of overdose as well as the risks of infectious-disease transmission and engagement in criminal activities. Nevertheless, MATs have been adopted in less than half of private-sector treatment programs, and even in programs that do offer MATs, only 34.4 percent of patients receive them. Ongoing NIDA research is working to develop improved strategies for the implementation of these evidence-based interventions. This includes research to tailor treatment interventions to individuals with unique needs, including those in the criminal justice system or with HIV.

Question. Are there barriers to research?

Answer. NIDA research is working to address the barriers mentioned above related to the development of new mediations (described in part c.) and increasing implementation of evidence based treatment strategies (described in part d).

QUESTIONS SUBMITTED BY SENATOR JACK REED

OVERDOSE PREVENTION

Question. On June, I introduced the Overdose Prevention Act to help combat the growing number of overdose deaths. Last year in Rhode Island, nearly 250 people died due to an overdose and so far this year, there have been over 130 overdose deaths. Unfortunately, this is not unique to Rhode Island. We are seeing a spike in overdose deaths due to heroin and prescription drugs across the country. My legislation would expand access to naloxone, which reverses the effects of an overdose. What is NIDA doing to look at ways we can better prevent overdose deaths?

Answer. NIDA is an active partner in the initiative of the Secretary of Health and Human Services to address the complex problems of prescription opioid and heroin abuse, and the associated overdose epidemic, through improving education of healthcare providers on pain management and proper opioid prescribing; increasing the implementation of evidence-based prevention and treatment strategies; and increasing availability and adoption of the effective overdose-reversal drug naloxone (see part b. below).

Over-prescription of opioid medications has been a major driver of the opioid epidemic, and thus improving how physicians and other healthcare providers treat pain is a crucial part of preventing opioid abuse. Unfortunately, pain management is inadequately covered in most medical, dental, and nursing schools, and for the past two decades there has been an overreliance on powerful, highly addictive opioids even in chronic non-cancer pain conditions for which these drugs may not be ideal. Thus as part of the NIH Pain Consortium, NIDA supports 13 Centers of Excellence in Pain Education (CoEPEs), which develop and disseminate pain curricula to improve how healthcare professionals are taught about pain and its treatment. In addition, the NIDAMED initiative develops continuing medical education (CME) courses for physicians and other healthcare providers on pain treatment as well as how to identify and address drug abuse and addiction. NIDA is also actively researching alternative approaches to pain treatment, including abuse-resistant formulations of existing opioid medications, non-opioid mechanisms for pain control (such as the endocannabinoid system), and nonpharmacological (non-drug) approaches.

Treating opioid use disorders is another crucial component of the strategy to end the opioid epidemic. Effective treatments exist for these opioid use disorders, yet they are highly underutilized across the United States. Ample research shows that, when used at sufficient dose and for sufficient duration, three medications—methadone, buprenorphine, and extended-release naltrexone—are highly effective at reducing opioid use, keeping patients in treatment, and reducing transmission of infectious diseases such as HIV and hepatitis C as well as criminal justice involvement. Ongoing NIDA research is working to develop improved strategies for the implementation of these evidence-based interventions.

Question. Do you think expanding access to naloxone can play an important role in reducing overdose deaths?

Answer. Yes, expanding naloxone access is one of the most important measures that can be taken to prevent death from opioid overdose. Experimental pilot projects distributing naloxone to first responders, opioid users, their families, and potential bystanders has shown it to be a lifesaver in communities where it has been implemented. Defying the expectations of some critics, these programs have reduced overdose deaths without causing an increase in opioid abuse in those communities.

Last year, FDA approved an auto-injector to make naloxone somewhat easier to administer, however most pilot programs have continued to use naloxone syringes fitted with an atomizer to enable the drug to be sprayed in the nostrils (intranasal

administration), as this is less expensive and the easiest mode of administration for laypeople. Administering a drug formulated for injection intranasally is not ideal, however. Thus NIDA is working with FDA and drug manufacturers to support the development and approval of an FDA-approvable formulation of intranasal naloxone that would match the pharmacokinetics (i.e. how much and how rapidly the drug gets into the body) of the injectable version. In executing this project NIDA partnered with two small companies, AntiOP and Lightlake Therapeutics, which have each partnered with larger pharmaceutical companies, Indivior and Adapt Pharmaceuticals (respectively). Both Indivior and Adapt filed new drug applications (NDAs) with the FDA this year.

CONCLUSION OF HEARING

Senator BLUNT. Thank you for being here.

The subcommittee stands in recess.

[Whereupon, at 11:58 a.m., Wednesday, October 7, the hearing was concluded, and the subcommittee was recessed, to reconvene subject to the call of the Chair.]